Karolinska Institutet

Institutionen för Mikrobiologi, Tumör och Cellbiologi

Regulation of *Plasmodium falciparum* virulence genes and immune response to surface antigens in placental malaria

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Rockefeller, Nobels Väg 11, Karolinska Institutet

Fredagen den 16/12, 2011, kl 13.15

av

Kim Brolin

Huvudhandledare:
Professor Qijun Chen
Karolinska Institutet
Institutionen för Mikrobiologi,
Tumör och Cellbiologi

Bihandledare:
Docent Stephen Rogerson
Melbourne University
Department of Medicine

Dr. Kristina Persson
Karolinska Institutet
Institutionen för Mikrobiologi,
Tumör och Cellbiologi

Fakultetsopponent:
Professor Thor Theander
Köpenhamns Universitet
Avdelningen för Internationell Hälsa,
Immunologi och Mikrobiologi

Betygsnämnd:
Docent Lena Åslund
Uppsala Universitet
Institutionen för Genetik, Immunologi och patologi

Professor Rolf Ohlsson
Karolinska Institutet
Institutionen för Mikrobiologi,
Tumör och Cellbiologi

Professor Marita Troye Blomberg
Stockholm Universitet
Avdelningen för Immunologi, WGI

Stockholm 2011

ABSTRACT

Malaria infection caused by the parasite *Plasmodium falciparum* is a deadly torment, especially for young children and pregnant women residing in sub-Saharan Africa. Much of the parasites virulence is due to its ability to constantly vary the adhesive molecules expressed on the surface of infected red blood cells (iRBCs). This antigenic variation permits the parasite to successfully sequester in various organs and tissues, thereby causing adverse effects and the clinical symptoms of malaria as well as enabling evasion of the host immune response. However, protective antibodies against surface exposed antigens are developed via exposure to infection, explaining the partial immunity seen in adults living in endemic areas. Another important aspect of the deadliness of *P. falciparum* is its astounding ability to successfully proliferate and multiply within the RBC. Numerous genes encode proteins that allow the daughter merozoites to effectively invade new RBC. While antigenic variation is a well-studied phenomenon in pathogens, very little is known concerning the regulation of invasion genes. In this thesis, we have explored both epigenetic regulation and immune recognition of *P. falciparim* virulence genes.

The *var* gene encoded *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) VAR2CSA is the main adhesin involved in placental malaria. We investigated the differential recognition of various VAR2CSA DBL-domains by immune sera from pregnant women and found DBL5ε to be widely recognized in a gender and parity-specific pattern. Further studies revealed that while the affinity of acquired antibodies to DBL5ε is similar between primigravidae and multigravidae, HIV co-infection impair the binding capability of these antibodies in women in their first pregnancy. Transcriptional regulation of *var2csa* as well as other *var* genes has been shown to be a complex and tightly regulated process. Our studies on duplicated *var2csa* paralogs in the *P. falciparum* strain HB3 revealed simultaneous transcription of both alleles. This suggests a less strict *var* gene regulation than previously thought and questions whether PfEMP1s are mutually exclusive expressed. Our findings support the presence of an active *var* gene expression site in the nuclear periphery but also suggest additional layers of gene regulation to be important, such as trans-factors and histone modifications. The five *P. falciparum* histone deacetylases are interesting therapeutic targets but have not been extensively characterized. By using reverse genetics techniques, we were able to create a conditional knockdown of the class II histone deacetylase PfHda1. The phenotypic change upon PfHda1 knockdown suggests this protein to be essential for cell cycle progression and successful proliferation but also for differential expression of invasion ligands. Moreover, dysregulation of *var* gene expression is seen in PfHda1 knockdown parasites, which provides insight into mechanisms behind virulence gene regulation in the context of histone modifications. To conclude, we here present a multi-faceted study of mechanisms behind multi-family gene expression important for parasite virulence and explore the complexity of antibody acquisition to VAR2CSA.

ISBN 978-91-7457-586-6