Malaria Introduction

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Overview

• Background and impact on the world

• Mechanism behind the disease

• Special case – Pregnancy Associated Malaria.

• Your goal for the next hours.
Malaria

• Caused by a parasite of the genus *Plasmodium*, mainly:
  
  • *Plasmodium falciparum* (Africa)
  
  • *Plasmodium vivax* (Asia and America)

• Transferred to humans by a mosquito of the genus *Anopheles*

Sources: WHO and Centers for Disease Control and Prevention (CDC)
Malaria - a serious problem

- 243 million cases / 863,000 deaths in 2008
- Only matched by HIV (2.1 mill. deaths (2007)) and TB (1.6 mill. deaths (2005))
- Most victims are children under the age of 5 in sub-Saharan Africa

Source: WHO
Infected Red Blood Cells

Source: scienceblogs.com
Malaria - Life cycle

Sources: Miller, Nature, 2002 and CDC
Malaria - immunological targets

Pre-erythrocytic stage (CSP, SSP2 and LSA1)

Merozoite RBC-invasion (MSP1 and AMA1)

Vector transmission antigens

iRBC adherence (PfEMP-1)

Sources: Miller, Nature, 2002 and Malaria Vaccine Initiative (MVI)
Blood stage parasites

Vascular endothelium
Blood stage parasites

Vascular endothelium

PfEMP1
Blood stage parasites
Blood stage parasites

Spleen

Vascular endothelium

PfEMP1
PfEMP1 variant antibodies

- Encoded by the *var* gene family
- The *Plasmodium falciparum* genome contains ~60 copies of the *var* gene
- Extremely diverse

Source: Miller, Nature, 2002
PfEMP1 domain structure

Plasmodium falciparum erythrocyte membrane protein - PfEMP1

Domain structure

DBL-1α CIDR1 DBL-2β DBL-3γ DBL-4δ CIDR2 ATS
Exon-1
Exon-2

Multi-adhesive semi-conserved headstructure

DBL domains are described by the position of the domain on the particular var gene (DBL1-5) and the greek letter identifies the homology type groups

DBL = Duffy Binding Like domain - polymorphic
CIDR = Cysteine Rich Inter domain Region - polymorphic
ATS = Acidic Terminal Segment

Highly polymorphic interdomain region
Conserved cytoplasmic domain

Source: Adapted from Wahlgren et al (sites.huji.ac.il/malaria/maps/PfEMP1.html)
Pregnancy associated malaria (PAM)

- Maternal anaemia and death (~10,000 cases/year in Africa)

- Perinatal deaths (~200,000 cases/year in Africa)

- Spontaneous abortion

- Stillbirth

- Premature delivery

- In some endemic regions, 40% of all newborns have low birth weight caused by PAM

Sources: Greenwood BM (2005), WHO
Pregnancy associated malaria (PAM)

- Caused by PfEMP1 binding to CSA in placenta
- PfEMP1 variant: VAR2CSA

Source: Miller, Nature, 2002
PfEMP1: VAR2CSA

- Upregulated in iRBC adhering to CSA and in placental isolates

- Highly conserved between falciparum strains compared to most other var genes (nucleotide sequence diversity is 10-30 %)

Goal for this afternoon

- Combine all your knowledge of bioinformatics
- Find a vaccine candidate for pregnancy associated malaria
- Help the world and save lives of children
- All in less than 3 hours