Malariology: Biology of the Parasite

Nirbhay Kumar, PhD
Impact

• Worldwide
  – >2.3 billion people at risk
  – 300 to 500 million cases annually
  – 1.5 to 2.7 million deaths annually

One death every 20 to 30 seconds, somewhere in the world
Malaria: *Plasmodium* Species of Human Disease

- *P. falciparum* (malignant, TERTIAN)
- *P. vivax* (benign, TERTIAN)
- *P. ovale* (TERTIAN)
- *P. malariae* (QUARTAN)

Malaria parasites are highly species specific. No animal reservoir for human malaria parasites.
The Infective stage (SPOROZOITE) transmitted by female anopheline mosquito

Source: Nirbhay Kumar
• Sporozoites invade hepatocytes
  – \( t_{\frac{1}{2}} < 30 \text{ minutes} \)
• Undergo asexual development over the next 7-10 days
• Results in 20,000 – 30,000 fold increase in parasite numbers
• Merozoites released then invade RBCs (erythrocytes)
• \( P. \text{ vivax} \) and \( P. \text{ ovale} \) parasites produce hypnozoites (dormant parasites) which are responsible for relapse of malaria
Relapse versus Recrudescence

• Relapse: (*P. vivax* and *P. ovale*)
  – Presence of dormant hypnozoites in the liver

• Recrudescence: (All 4 species)
  – Reappearance of blood forms of parasites (drug resistance)
A Typical Asexual Cycle

• Merozoites attach to rbc, orient to apical end, invaginate into RBC by forming rbc membrane pocket called parasitophorous vacuole.

• Merozoites invade RBCs and develop into ‘RING’ forms

• Rings develop into TROPHOZOITES (contain microscopic heme crystal)

• Trophozoites replicate nuclear material to form SCHIZONTs (form with more than one nucleus)

• RBCs are lysed and Merozoites (12-32) released continue the RBC cycle

• (Tertian malaria – 48 hour cycle for Pf, Pv, Po), and (Quartan malaria–72 hour cycle for Pm)
Early Stages of Red Blood Cell Invasion by the Malaria Merozoite

1. Initial Attachment & Reorientation
   - P. vivax
   - PvRBP-1
   - PvRBP-2
   - Pyoellii
   - Py235?
   - MSP-1 complex?
   - AMA-1?
   - MAEBL?

2. Irreversible Attachment & Junction Formation
   - Secretion of microneme contents (e.g., DBL-EBP)
   - Rhopty discharge
   - High affinity adhesion mediated by DBL-EBP?
   - Inward motion driven by actomyosin motor

3. Parasitophorous Vacuole Formation & Invasion
   - Further rhoptry and microneme discharge
   - Release of dense granule contents ( PfSUB-1 & PfSUB-2)
   - Vectorial trafficking, proteolytic processing & shedding of DBL-EBP
   - Proteolytic processing/shedding of MSP-1 complex

Adapted by CTLT from Parasitology Today
Classic Every Other Day Malaria Fevers

“Tertian” *P. vivax*

Adapted from Thayer and Hewetson
Johns Hopkins Hosp Reports V 1895 p. 3-224
Typical Malaria Paroxysms

• Three stages
  – **COLD**: Chilly feeling followed by rising body temperature (headache/nausea/vomit)

  – **HOT**: High temperature 39 to 40.5 °C

  – **SWEATING**: Falling temperature is accompanied by sweating (fatigue and weakness)
Pathological Complications of P. falciparum Malaria

- **Uncomplicated**
  - Fever
  - Parasitemia
  - Anemia

- **Complicated (severe) malaria**
  - Cerebral malaria (coma)
  - Severe anemia
  - Hypoglycemia
  - Renal failure
  - Electrolyte disturbances
  - Jaundice
  - Lactic acidosis
  - Etc. Etc.
Knobs on surface

Adherent parasites in brain
Cytoadherence (Sequestration)

• Binding of **TROPHOZOITE** & **SCHIZONT** infected RBCs to endothelial cells in post-capillary venuels in the deep tissues.

• The binding is thought to be mediated by parasite proteins in the electron-dense structures defined as **KNOBS**

Rosetting

• Binding of RBCs containing parasites (mixed stages) with uninfecte RBCs
Malaria Parasites Use Two Hosts

• A **human** where it causes the disease malaria

• A **mosquito** which it uses as a vector
Sexual Development

Asexual Stages -> Sexual Stages

Gametocyte (male and female sexual stages) development is crucial to transmission
Exflagellation (Emergence of Male Gametes)

Female Gametocyte

Male Gametocyte

GAMETES

ZYGOTE

8 male gametes from a single gametocytes in <10 min (XANTHURENIC ACID – exflagellation factor)

Source: Nirbhay Kumar
Innate Resistance Mechanisms
(Nonimmunological Mechanisms of Refractoriness)

**Hemoglobinopathies** (>300 in humans, most due to a single amino acid change in the hemoglobin molecule)

- Hbs (sickle cell Hb), Autosomal recessive (β-6 GLU to VAL)
- HbC (β-6 GLU to LYS)
- HbE (β-26 GLU to LYS)
- HbF (α/γ as compared to α/β in normal Hb)
- The Thalessemias (imbalance of α and β globin chains)

Cont. . .
Innate Resistance Mechanisms (Nonimmunological Mechanisms of Refractoriness)

**RBC enzyme deficiency**
- Glucose-6-phosphate dehydrogenase (G6PD)

**RBC surface components**
- Glycophorins (P. falciparum)
- Duffy blood group (P. vivax) (West Africana are Duffy –ve)

**RBC Cytoskeleton abnormality**
- (abnormal Band 3 protein)
- Ovalocytosis (elliptical red cells, PNG)

Cont. . .
Innate Resistance Mechanisms
(Nonimmunological Mechanisms of Refractoriness)

Sickle-cell hemoglobin (HbS)

- SC – trait in heterozygotes (AS)
- SC- anemia in homozygotes (SS) (Fatal prior to reproductive age)
- Gene frequency of AS is >>20% in Nigerian population and ~10% in Afro-Americans

PARASITES DIE DUE TO LACK OF OXYGEN and OTHER CAUSES