Plasma microvesicles in cerebral malaria: actors in the disease progression and potential biomarkers?

Valéry Combes
Microvesicles and Malaria Group
CEREBRAL MALARIA

>430,000 deaths in 2015, 90% children < age of 5
CEREBRAL MALARIA

- Major lethal complication of malaria infection (=infection of red blood cells by *Plasmodium falciparum* parasite)
- In sub-Saharan Africa: children under 5
- In South-East Asia: young adults
- Small vessels in the brain are distended by accumulation of infected red blood cells
- Brain swelling and small haemorrhages are features of the disease
• Without treatment: 100% fatal
• With treatment: 70 to 80% survival
• Among survivors: ~20% long-term sequelae (motor and cognitive impairment)
mechanisms?
STUDYING THE PATHOGENESIS OF CEREBRAL MALARIA – BASIC RESEARCH

Human samples: plasma of infected patients with *Plasmodium falciparum* (various stages of the disease)

*In vitro* modelling: co-culture of human cells to reproduce the disease

Mouse model: model for paediatric cerebral malaria and test of potential hypotheses
CEREBRAL MALARIA DIAGNOSIS AND NEED FOR BIOMARKERS

Understanding pathogenesis of the disease will help design new drug targets and provide efficient adjunct therapies to prevent death and complications

- Early diagnosis is essential for a proper treatment
- Few reliable markers of severe disease
- Markers of mortality and morbidity should help prevent death and identify neurological deficit
Microparticles/Microvesicles: Novel mechanisms of cell-cell communication

- Small elements (<1 µm) produced from the plasma membrane
- Detected in the blood circulation
- Display functional properties
- Can modify the behaviour of the target they interact with
- Associated to many diseases
MICROVESICLES IN PATHOLOGY

Haematologic / thrombotic disorders
- Thrombotic Thrombocytopenic Purpura (Jimenez, 2003), Idiotypic Thrombocytopenic Purpura, Heparin Induced Thrombocytopenia, stroke, systemic lupus erythematosus (Combes, 1999)
- Sickle cell disease, thromboembolism (Chirinos 2005)
- Pre-eclampsia (Combes et al., 2003)
- Cardiovascular diseases (Wagner 2003)

Neurological disorders
- Cerebral Malaria (Combes et al., 2004, 2005, 2006)
- Multiple Sclerosis (Jimenez 2005, Zinger 2016)

Infections
- malaria, sepsis, HIV, Ebola & haemorrhagic viruses, Chlamydia ...

Cancer
- metastasis
MAIN HYPOTHESIS

Microvesicles and their content represent a disease signature and could provide biomarkers for early detection of complications.
**upstream**

- microvesicle biogenesis

**downstream**

- pathogenesis
- disease severity
- susceptibility to disease

Functional properties
Composition (proteins, lipids, mRNA, miRNA) => biomarkers

**vesiculating cell** ➔ **microvesicles** ➔ **target cell**

functional changes

2 hr
IMPLICATION OF MICROVESICLES IN CM PATHOLOGY

- Endothelial microvesicle numbers are increased in CM patients in Malawi (Combes et al, JAMA, 2004)

- Increased released of all types of MP in CM patients in Cameroon (Pankoui-Mfonkeu et al, PLoS ONE, 2010)

  => MP numbers associated with the severity of the disease

- Platelet-MP enhance PRBC adherence to brain EC (Faille et al, FASEB J 2009)

- Red blood cell microvesicles carry parasite proteins, activate macrophages and stimulate immune response in murine CM (Couper et al. Plos Pathogens 2010)
IMPLICATION OF MICROVESICLES IN CM PATHOLOGY


- Microvesicles exhibit pathogenic effects (Combes et al, Am J Pathol 2005, El-Assaad Plos Path 2014)

- Protein cargo of plasma microvesicle (Tiberti, submitted)
  - reflects the pathological state of the mouse
  - consists of biologically active proteins
  - is significantly associated to pathways and functions involved in CM pathogenesis
POTENTIAL OF MY ONGOING RESEARCH

Health care

- Microvesicles are present in the plasma and other body fluids: easy access
- Targetting the production of microvesicles can improve patient status
- Find a signature of the disease can help predict complications
- Detection by rapid point-of-care test of microvesicles in body fluid

Applied research

- Improving the purification/detection of microvesicles and developing an approach that can be applied to various diseases (commercial kits exist to extract exosomes from body fluids but nothing exist for microvesicles)