**University of Fribourg / Faculty of Science and Medicine / Department of Oncology, Microbiology and Immunology**

# CHARACTERIZATION OF HOST-PATHOGEN INTERACTIONS DURING BLOOD-STAGE HUMAN MALARIA

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Malaria, caused by parasites of the genus *Plasmodium* and transmitted by means of a bite of an infected female *Anopheles* mosquito, is a devastating disease with tremendous challenge for developing countries. Although the parasite has a complicated life cycle, it is well accepted that the exponential growth of the parasites in the blood is responsible for almost all the clinical symptoms of malaria and the associated morbidity and mortality. Hence, to efficiently prevent severe/fatal malaria, tight control of parasitemia is essential. Therefore, a comprehensive analysis of host-pathogen interactions during the blood-stage is urgently required to identify novel points of attack for drug design.

In the first part of the thesis, we improved a protocol for the efficient purification of *falciparum*-infected red blood cell derived extracellular vesicles, a major weapon of the parasites to communicate with each other and to manipulate immune defense systems of the host.
In the second part, we determine the lymphocytes subset and cytotoxic mechanisms that restrict the deadly growth of blood-residing *P. falciparum.*

The results contained in this thesis provides evidence that (1) during blood-stage malaria, extracellular vesicles represent a crucial tool for parasite-host communication and should be considered as important new biomarkers and potential drug targets. And (2) a particular subset of innate lymphocyte, the γδ T cells, expands and gains high cytolytic potential by upregulating their cytotoxic effector proteins and IFN-γ upon activation with *Plasmodium* culture supernatant. In addition, these activated killer cells specifically recognize, bind and kill *Plasmodium* in red blood cells via the transfer of the granzymes that is mediated by perforin and granulysin in a stage-specific manner. Finally, the discovery of protein substrates within the plasmodial proteome that were efficiently destroyed by granzyme B (GzmB), not only supports the hypothesis that the delivery of active GzmB into the parasite is the driving force for the observed decrease of parasite viability but may provide novel targets for therapy approaches.

Overall, this PhD thesis not only dissects an evolutionary shaped host-pathogen interaction with broad implications to the understanding of plasmodial pathogenesis, but also provides the necessary base for the rational development of preventive or therapeutic intervention strategies.

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