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Abstract

Cross-talk between inflammation, coagulation and oxidative stress in malaria during pregnancy

Malaria infection caused by *Plasmodium falciparum* infection during pregnancy produces profound placental dysfunction, leading to poor birth outcomes such as intrauterine growth restriction and preterm labor, yielding low birth weight infants. "Placental malaria" is characterized by maternal inflammatory responses, including cellular infiltrate in the placenta, hypercoagulation with excessive fibrin deposition, oxidative stress, and cell death. Understanding these phenomena – how they are initiated, propagated, and interrelated to yield placental dysfunction – forms the foundation of the work in my laboratory. We use a combination of human samples (from women naturally exposed to malaria in Kenya), *in vitro* culture systems, and mouse models to probe mechanisms in placental malaria pathogenesis.

Previous work in my laboratory has shown that genetic disruption of the extrinsic coagulation pathway and the inflammatory mediator, tumor necrosis factor (TNF), independently improve pregnancy outcomes in C57BL/6 mice infected with *Plasmodium chabaudi* in early gestation. In the absence of treatment, these mice experience pregnancy loss at mid-gestation. Similarly, therapeutic intervention to suppress coagulation, inflammation, and oxidative stress also independently improve pregnancy outcomes in this model. However, most of these interventions do not completely restore pregnancy success. We hypothesize that the three pathways – coagulation, inflammation and oxidative stress – syngerize to mediate pregnancy compromise in this model by impacting the placenta. This project, which is part of the ongoing research of a PhD student, aims to assess the efficacy of combination treatments and multiple genetic knockouts in maximizing pregnancy success in the context of malaria infection.

Aim 1: To assess the ability of combination drug therapy with drugs to combat mitochondrial oxidative damage and coagulation to improve pregnancy outcomes in C57BL/6 mice infected with *Plasmodium chabaudi* in early gestation.

Aim 2: To characterize pregnancy success in mice with both genetic depletion of TNF (*$TNF^{-/-}$)* and cell specific depletion of tissue factor (Tie2-cre, *$F3^{flox/flox}$, "TFΔEc")* infected with *Plasmodium chabaudi* in early gestation.

The proposed project for an FVSP student is to work in the above-described mouse models to advance the work proposed in the Aims above. Because this work is ongoing, it is not clear which Aim will take precedence or if work on both will be possible. Importantly, the double mutant mice described in Aim 2 are under development currently, and it is not possible to predict when adequate numbers of these mice will be available for experimentation.

To contribute to these projects, the FVSP student will learn how to mate mice, initiate malaria infections, assess parasitemia and other clinical markers of infection and pregnancy, deliver drug treatments (depending on the Aim), and perform necropsies (anesthesia and terminal surgery). Time permitting, the student will process placental samples from these experiments for histology and immunohistochemistry and/or isolate messenger RNA for gene expression experiments.