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Placental Malaria: From Infection to Malfunction

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Malaria during pregnancy is a major factor in infant morbidity and mortality. In this issue of *Cell Host and Microbe*, Conroy et al. (2013) propose that C5a, a product of complement cascade activation, counteracts the placental vascular remodeling response induced by *Plasmodium* infection and contributes to fetal growth restriction.

In Māori tradition, the placenta (*whenua* in the language of Māori) is buried upon birth to establish a link between the land (likewise called *whenua*) and the newborn. Both types of *whenua* nourish: "One allows the foetus to become a baby with all the potential to become a strong and healthy adult, and the other sees that person develop and grow, make their contribution to society and then be 'born' into the spirit of the world" (Head and Head, 2003). Although the placenta is credited with the developing fetus, surprisingly little is known about critical molecules and physiological parameters that control the functional efficacy of this fast-growing organ and determine pregnancy success.

Fetal growth restriction is a severe consequence of malarial disease during pregnancy and thought to result largely from placental insufficiency. Much research has been centered on the pathogenic role of ligand-receptor interactions between the *Plasmodium*-infected erythrocyte and placental tissues (reviewed by Duffy and Fried, 2005). Parasite antigens expressed on the surface of infected erythrocytes are thought to contribute to accumulation of parasitized cells in the placenta. The best example is var2csa, member of the *var* (variable surface antigen) gene family that is selectively expressed by infected erythrocytes that accumulate in the placenta (Salanti et al., 2003). VAR2CSA has strong affinity to the glycosaminoglycan chondrotin sulfate A (CSA or C4S) present in high amounts in the intervillous space and on the surface of syncytiotrophoblasts, which contact the maternal blood. The current pathogenesis model is focused on linking placental sequestration of infected erythrocytes to a series of inflammatory events that can reduce fetal growth. Cytoadhesion of infected erythrocytes can activate syncytiotrophoblast cells to secrete chemokines, which attract maternal inflammatory cells (Lucchi et al., 2008). But how does inflammation impair maternal-fetal exchange? Little attention has been paid to the impact of malaria on physiology of the fast-developing placenta that in the course of infection may contribute to placental insufficiency. Recently the pathogenesis paradigm was challenged by work that addresses the role of angiogenesis factors (reviewed by Conroy et al., 2011), the coagulation cascade (Avery et al., 2012), and placental microcirculation (Moraes et al., 2013).

In this issue, Conroy et al. (2013) investigate potential links between inflammation, angiogenesis alterations, and fetal growth restriction in pregnancy-associated malaria. They focus on activation of the complement cascade, previously shown to impair placental vascular remodeling in mouse models of miscarriage or fetal growth restriction (reviewed by Girardi, 2008). Complement cascade activation by immune complexes in the placenta may indirectly contribute to inflammation. C5a—a protein fragment released by the activation of C5 complement component—was shown to be implicated in tissue injury by inducing release of reactive oxygen species of C5a-activated neutrophils. Nevertheless, in antibody-independent models of unsuccessful pregnancy, inflammatory cells indirectly generate C5a fractions that activate monocytes to produce soluble vascular endothelial growth factor (sVEGF), an inhibitor of VEGF. This deregulation of angiogenic factors is hypothesized to disturb the developing placental vascularization and as a consequence impeding babies of getting appropriate nurturing.

The study by Conroy et al. (2013) tackles this issue and provides epidemiological data and compelling experimental

evidence that placental vascular insufficiency is a cause of low birth weight in placental malaria and is partially mediated by C5a. The authors observe that elevated C5a levels in women infected with *Plasmodium falciparum* during pregnancy are associated with low-weight babies and altered levels of angiogenic factors. This causative chain is demonstrated using C5a receptor (C5aR)-deficient mice, where *P. berghei* infection during pregnancy resulted in decreased placental arterial vascular resistance and correlated with improved fetal viability and birth weight. Impressively, this was verified by 3D micro-CT placental scanning, allowing the visualization of significantly increased vascular branching in the absence of C5a. Usage of C5a-deficient mice was key to distinguish the placental proangiogenic response to malaria infection, from the antiangiogenic response resulting from C5a activity. High levels of C5a elicited by the malaria infection tilt the balance of these two concurrent responses, presumably impairing development of the feto-placental arterial vasculature and leading to increased arterial resistance.

These observations imply that reduction of intraplacental blood circulation is harming fetal nurturing and suggest that reduced placental perfusion elicited by other mechanisms involved in the response to infection may also contribute to fetal growth restriction. Using different mouse and parasite strains we have observed decreased placental vascularization and reduction of the maternal blood space in the labyrinth region of *Plasmodium*-infected placentas (Rodrigues-Duarte et al., 2012). Maternal blood microcirculation in the mouse placenta was recently shown to promote sequestration of *P. berghei*-infected erythrocytes in maternal blood spaces with reduced or no flow (Moraes et al., 2013). The C5a effect on angiogenesis could aggravate maternal blood perfusion in infected placentas, favoring parasite sequestration, amplifying the placental response mechanisms, and impoverishing *te whenua* (Figure 1). Excessive fibrin deposition in the infected placenta has been associated with a dramatic upregulation of tissue factor (TF) resulting in a procoagulant and antifibrinolytic response (Avery et al., 2012). These authors claim that therapeutically targeting hemostasis deregulation improved placental pathology and ameliorated pregnancy outcomes. Remarkably, as shown by Conroy et al. (2013), antibody inhibition of C5a-C5aR signaling improved fetal weight of infected pregnant mice. This highlights the C5a-C5aR signaling axis as a target of therapeutics that may enable restoration of placental sufficiency to protect fetal growth and viability in the presence of malaria infection. Focusing the research on placental insufficiency is conveying the notion that poor pregnancy outcomes of malaria infection might be mitigated by therapeutically restoring placental functional efficacy independent of antiparasite therapies.

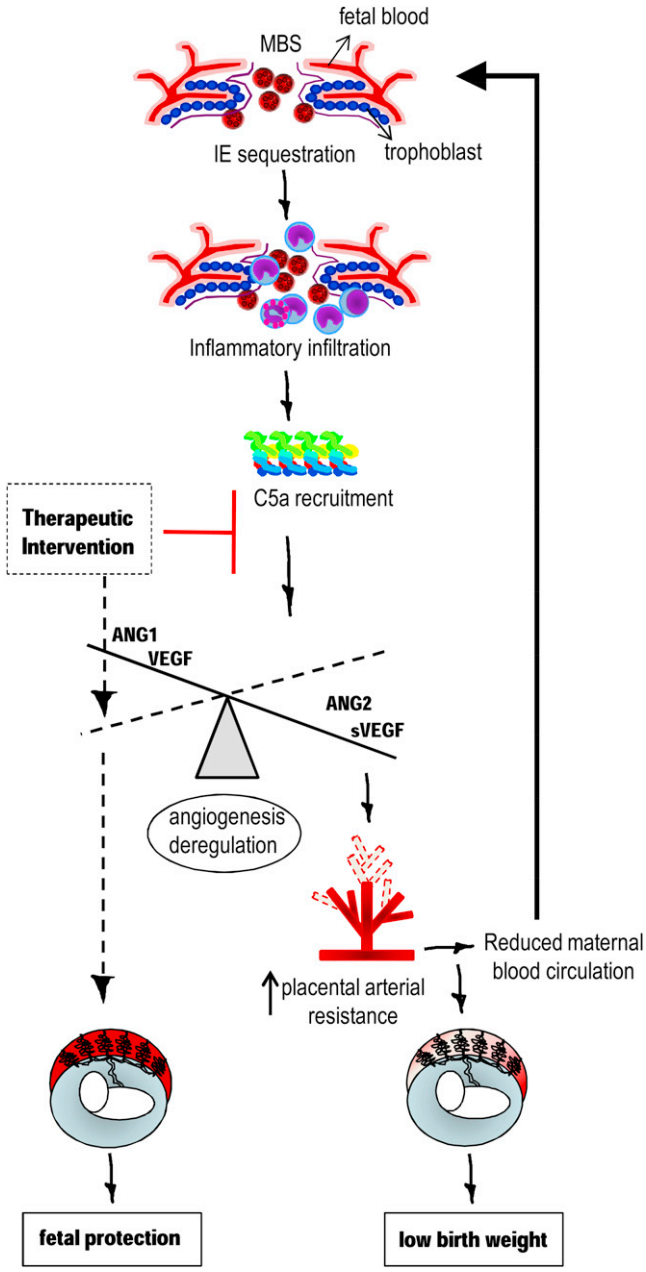

Figure 1. *Plasmodium* Infection and Placenta Malfunction
Accumulation of infected erythrocytes (IE) in maternal blood spaces (MBS) leads to inflammatory mononuclear cell recruitment. In this inflammatory mellieu C5a proinflammatory activity contributes to imbalance of angiogenic factors. As a result of this antiangiogenic response, intraplacental vascular resistance increases impairing placental perfusion. Altered hemodynamics in the infected placenta conditions maternal blood flow, which promotes infected erythrocyte accumulation. This cycle amplifies the inflammatory response leading to placental dysfunction and impacting fetal growth. Therapeutic intervention aiming to decrease C5a generation/signaling could contribute to promote a proangiogenic response and restore placental perfusion counteracting the deleterious effects of placental malaria in the pregnancy outcome.

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