

Role of monocyte-acquired hemozoin in suppression of macrophage migration inhibitory factor in children with severe malarial anemia.

[Awandare GA](#), [Ouma Y](#), [Ouma C](#), [Were T](#), [Otieno R](#), [Keller CC](#), [Davenport GC](#), [Hittner JB](#), [Vulule J](#), [Ferrell R](#), [Ong'echa JM](#), [Perkins DJ](#).

Source

Department of Infectious Diseases & Microbiology, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, 603 Parran Hall, Pittsburgh, PA 15261, USA.

Abstract

Severe malarial anemia (SMA), caused by *Plasmodium falciparum* infections, is one of the leading causes of childhood mortality in sub-Saharan Africa. Although the molecular determinants of SMA are largely undefined, dysregulation in host-derived inflammatory mediators influences disease severity. Macrophage migration inhibitory factor (MIF) is an important regulator of innate inflammatory responses that has recently been shown to suppress erythropoiesis and promote pathogenesis of SMA in murine models. To examine the role of MIF in the development of childhood SMA, peripheral blood MIF production was examined in Kenyan children (aged <3 years, n = 357) with *P. falciparum* malarial anemia. All children in the study were free from bacteremia and human immunodeficiency virus type 1. Since deposition of malarial pigment (hemozoin [Hz]) contributes to suppression of erythropoiesis, the relationship between MIF concentrations and monocytic acquisition of Hz was also examined in vivo and in vitro. Circulating MIF concentrations declined with increasing severity of anemia and significantly correlated with peripheral blood leukocyte MIF transcripts. However, MIF concentrations in peripheral blood were not significantly associated with reticulocyte production. Multivariate regression analyses, controlling for age, gender, and parasitemia, further revealed that elevated levels of pigment-containing monocytes (PCM) was associated with SMA and decreased MIF production. In addition, PCM levels were a better predictor of hemoglobin and MIF concentrations than parasite density. Additional experiments in malaria-naive individuals demonstrated that hemozoin caused both increased and decreased MIF production in cultured peripheral blood mononuclear cells (PBMC) in a donor-specific manner, independent of apoptosis. However, PBMC MIF production in children with acute malaria progressively declined with increasing

anemia severity. Results presented here demonstrate that acquisition of hemozoin by monocytes is associated with suppression of peripheral blood MIF production and enhanced severity of anemia in childhood malaria.