

## Oral 1731-1 - The role of alternatively activated (M2) monocytes in limiting NO bioavailability in falciparum malaria

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**Background:** We established earlier that NO has potent anti-malaria disease activity in humans. We have discovered a variety of mechanisms by which host NO bioavailability is decreased in children and adults with falciparum malaria (Weinberg et al., *Curr. Opin. Infect. Dis.* 21 (2008) 468–475, for review). The underlying process(es) causing changes in these factors with resultant low NO in malaria is not known. Monocytes-macrophages can be activated through the classical pathway (“M1”) with cytokines such as IFN- $\gamma$  and TNF, or through the alternative pathway (“M2”) with cytokines such as IL-4, IL-10, and IL-13. M1 cells are characterized by increased NOS2, NO, and superoxide production, while M2 cells have decreased NOS2 and NO production, increased arginase 1 expression, and increased expression of the scavenger receptor CD163 and the mannose receptor CD206 by monocytes.

Hypothesis: Monocytes in falciparum malaria patients are alternatively activated, and this activation contributes to the low NO bioavailability in malaria.

**Objective:** Determine the status of monocyte activation in Tanzanian children with falciparum malaria.

Methods: We studied the categories healthy control (HC, n=62), moderately severe malaria (MSM, n=54), and severe malaria (SM, n=50) (total n=166). We used real-time RT-PCR to measure PBMC mRNA for arginase 1 & 2, NOS2, and GTP cyclohydrolase 1; flow cytometry for monocyte surface CD163 & CD206; ELISA for plasma soluble CD163; and ELISA for plasmacytokine levels.

**Results:** Compared to HC subjects, patients with malaria had significantly higher PBMC arginase 1 mRNA, lower NOS2 mRNA, slightly higher GTPCH-1 mRNA, and unchanged arginase 2 mRNA; higher PBMC arginase 1 protein by immunoblot; higher plasma arginase enzyme activity and soluble CD163; higher monocyte surface CD206 and CD163; and higher plasma IL-10, IL-4, and IL-13. Overall, this pattern of changes we see in malaria patients is characteristic of alternatively activated (M2) monocytes.

**Conclusions:** Our results indicate presence of alternatively activated (M2) monocytes in children with falciparum malaria. We speculate that the M2 status of mononuclear phagocytes is a major factor underlying certain causes of low NO bioavailability in malaria. Preventing M2 development or reversing M2 status to either no activation or M1 activation status will likely be useful in preventing and treating malaria.

**Keywords:** Malaria; Monocyte; Alternative activation; M2; Nitric oxide; Arginase; Arginine.