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FIBRINOGEN AS BIOACTIVE SIGNAL MOLECULE IN THE IMMUNE REPONSE TO HEMOZOIN

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Malaria pigment hemozoin (HZ) released after schizont rupture is first phagocytosed by circulating resident phagocytes, where it modifies important monocyte functions like oxidative burst induction and release of pro-inflammatory cyto- and chemokines. We investigated the molecular interaction between HZ and monocyte showing the essential role of HZ-attached fibrinogen (FG) in ROS production, TNFα and MCP-1 release by human monocytes.

Native HZ was isolated from *P. falciparum in vitro*-cultures, and its protein pattern was analysed by a combined approach of proteomics and western blotting. HZ was differently treated to modify its protein composition and applied in *in vitro*-phagocytosis by human monocytes.

FG was revealed to be the most abundant protein firmly attached to native HZ, and seems to have a fundamental role in HZ interaction with the monocyte. In contrast to native HZ, FG-free HZ was not able to elicit monocytic oxidative burst, release of TNFα and MCP-1. Exposure of monocytes to HZ-bound FG resulted in an immediate increase of ROS production measurable already 2 min after contact, making the recognition of FG by a surface receptor with subsequent trans-membrane signalling most likely. Toll-like receptor 4 (TLR4) and β_2-integrin (CD11b/CD18) were found to be potential FG-receptors in HZ-exposed monocytes as concluded from lack of burst activation and reduced TNFα release in presence of blocking anti- TLR4 antibody, and an inhibition by 50% of MCP-1 pre-treating cells with a blocking anti CD11b antibody.

Present *in vitro* data provide strong evidence that recognition of FG on HZ was responsible for the first response of monocytes to malaria pigment, and might be useful for the host immune system to detect parasite products.