

MALARIA BLOOD STAGE PARASITES ACTIVATE HUMAN PLASMACYTOID DENDRITIC CELLS AND MURINE DENDRITIC CELLS THROUGH A TOLL-LIKE RECEPTOR 9-DEPENDENT PATHWAY

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A common feature of severe *Plasmodium falciparum* infection is the increased systemic release of proinflammatory cytokines that contributes to the pathogenesis of malaria. Using human blood, we found that blood stage schizonts or soluble schizont extracts activated plasmacytoid dendritic cells (PDCs) to up-regulate CD86 expression and produce IFN- α . IFN- α production was also detected in malaria-infected patients, but the levels of circulating PDCs were markedly reduced, possibly because of schizont-stimulated up-regulation of CCR7, which is critical for PDC migration. The schizont-stimulated PDCs elicited a poor T cell response, but promoted $\gamma\delta$ T cell proliferation and IFN- γ production. The schizont immune stimulatory effects could be reproduced using murine DCs and required the Toll-like receptor 9 (TLR9)-MyD88 signaling pathway. Although the only known TLR9 ligand is CpG motifs in pathogen DNA, the activity of the soluble schizont extract was far greater than that of schizont DNA, and it was heat labile and precipitable with ammonium sulfate, unlike the activity of bacterial DNA. These results demonstrate that schizont extracts contain a novel and previously unknown ligand for TLR9 and suggest that the stimulatory effects of this ligand on PDCs may play a key role in immunoregulation and immunopathogenesis of human *falciparum* malaria.

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A common feature of severe *P. falciparum* infection is the increased systemic release of proinflammatory cytokines that contributes to the pathogenesis of malaria. Using human blood, we found that blood stage schizonts or soluble schizont extracts activated plasmacytoid dendritic cells (PDCs) to up-regulate CD86 expression and produce IFN- α . The IFN- α production was also detected in malaria-infected patients, but the levels of circulating PDCs were markedly reduced, possibly because of schizont-stimulated up-regulation of CC chemokine receptor 7 (CCR7), which is critical for PDC migration. The schizont-stimulated PDCs elicited a poor T cell response, but promoted $\gamma\delta$ T cell proliferation and IFN- γ production. The schizont immune stimulatory effects could be reproduced using murine DCs, and required the Toll-like receptor 9 (TLR9)-MyD88 signaling pathway. Although the only known TLR9 ligand is CpG motifs in pathogen DNA, the activity of the soluble schizont extract was far higher than that of schizont DNA, and the activity was heat labile and precipitable with ammonium sulfate, unlike the