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Naturally acquired hemozoin by monocytes promotes suppression of RANTES in children with malarial anemia through an IL-10-dependent mechanism.

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Source

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Abstract

Regulated upon activation, normal T-cell expressed, and secreted (RANTES, CCL-5) is an important immunoregulatory mediator that is suppressed in children with malarial anemia (MA). Although pro-inflammatory (e.g., TNF-alpha, IL-1beta and IFN-gamma) and anti-inflammatory (e.g., IL-4, IL-10 and IL-13) cytokines regulate RANTES production, their effect on RANTES in children with MA has not been determined. Since intraleukocytic malarial pigment, hemozoin (Hz), causes dysregulation in chemokine and cytokine production, the impact of naturally acquired Hz (pfHz) on RANTES and RANTES-regulatory cytokines (TNF-alpha, IFN-gamma, IL-1beta, IL-4, IL-10, and IL-13) was examined. Circulating RANTES levels progressively declined with increasing levels of pigment-containing monocytes (PCM) ($P=0.035$). Additional experiments in cultured peripheral blood mononuclear cells (PBMC) showed that monocytic acquisition of pfHz (in vivo) was associated with suppression of RANTES under baseline ($P=0.001$) and stimulated conditions ($P=0.072$). Although high PCM levels were associated with decreased circulating IFN-gamma ($P=0.003$) and IL-10 ($P=0.010$), multivariate modeling revealed that only PCM ($P=0.048$, beta=-0.171) and IL-10 ($P<0.0001$, beta=-0.476) were independently associated with RANTES production. Subsequent in vitro experiments revealed that blockade of endogenous IL-10 significantly increased RANTES production ($P=0.028$) in PBMC from children with naturally acquired Hz. Results here demonstrate that monocytic acquisition of Hz suppresses RANTES production in children with MA through an IL-10-dependent mechanism.