Inhibition of erythropoiesis in malaria anaemia. Role of hemozoin and hemozoin-generated 4-hydroxynonenal

Inhibition of erythropoiesis in malaria anemia: Role of hemozoin and hemozoin-generated 4-hydroxynonenal

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Severe malaria anemia is characterized by inhibited/altered erythropoiesis and frequent presence of hemozoin (HZ)-laden bone-marrow macrophages. HZ mediates peroxidation of unsaturated fatty acids and production of terminal aldehydes such as 4- hydroxynonenal (HNE). Present data show that HZ-laden human monocytes inhibited growth of co-incubated human primary erythroid cells and produced HNE that diffused to co-incubated cells generating HNE-protein adducts. Co-incubated HZ or low-micromolar HNE inhibited growth of developing human erythroid cells interfering with cell-cycle without inducing apoptosis. Two critical proteins in cell-cycle regulation, p53 and p21, were increased and the retinoblastoma protein, central regulator of G1- to S-phase transition, was consequently hypophosphorylated. The resultant decrease of cyclin A and D2 expression retarded cell-cycle progression in both erythroid cells and the K562 cell line. As a second major effect, HZ and HNE inhibited the protein expression of transferrin receptor 1, Stem Cell Factor receptor (c-kit), interleukin-3 receptor and erythropoietin receptor, all crucial for erythroid growth. The reduced receptor expression and the impaired cell-cycle activity decreased cells expressing glycophorin A and hemoglobin. Present data confirm the inhibitory role of HZ, identify HNE as one inhibitory molecule and describe multiple molecular targets of HNE in erythroid precursors possibly involved in erythropoiesis inhibition in malaria anemia.