Role of hemozoin and hemozoin-generated 4-hydroxynonenal in the pathogenesis of malaria diserythropoiesis

Oleksii Skorokhod, Luisa Caione, Wanda Piacibello, Paolo Arese, Evelin Schwarzer

Dyserythropoiesis (DYS) plays an important role in malaria anemia (MA). DYS is characterized by 1) altered morphology of erythroid precursors in bone marrow (BM); 2) low reticulocyte response; 3) normal production of erythropoietin (EPO). In human BM the erythroblastic island (EI) is the elementary units of erythropoiesis in which a central macrophage (MAC) is surrounded by 15-20 differentiating erythroid cells. In MA, HZ-laden MACs in BM correlate with abnormal erythroid precursors. In EI, HZ-laden central MACs are very close to developing erythroid cells. HZ-laden MACs produce and export potent lipoperoxidation products such as 4-hydroxynonenal (HNE). We and others have shown that growth and differentiation of erythroid precursors were inhibited by HZ. Present data indicate that HZ-laden monocytes and HZ inhibited the development of erythroid cells and erythroid line K562 and generated HNE adducts on their surface. Co-incubated HZ and HNE recapitulated growth inhibition and reduced expression of glycophorin A, EPO and transferrin receptors in both erythroid cells and K562 cells. HZ and HNE did not induce apoptosis but inhibited erythroid cell proliferation by modifying cell cycle components. Incubation with HZ or supplementation with HNE reduced dividing cells (G2/M) by 70-50%, respectively, while cells arrested in G0/G1- and S-phase were correspondingly increased. Similar alterations in cell cycle were also present in HZ- and HNE-treated K562 cells **(Skorokhod et al, Inhibition of erythropoiesis in malaria anemia: role of hemozoin and hemozoin-generated 4-hydroxynonenal.Blood. 2010 Nov 18;116(20):4328-37. doi: 10.1182/blood-2010-03-272781).** In conclusion, present data confirm the inhibitory role of HZ, identify HNE as one inhibitory molecule, and describe multiple molecular targets of HNE possibly involved in the mechanism of malaria dyserythropoiesis.