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Pro-stimulatory Potentials of Methemoglobin in Inflammation during Cerebral Malaria through Heme Polymer Formation

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Cerebral malaria (CM), a severe form of malaria causes life threatening complication. Methemoglobin (MetHb), released from infected RBC causes inflammation due to its ability to produce free radicals. MetHb can catalyze heme to heme polymer formation in the presence of hydrogen peroxide utilizing its peroxidase activity (R2=0.9722). More-Over, peroxidase inhibitors and the substrate inhibits heme polymer formation further confirm the role of peroxidase activity in polymerization process. Methemoglobin process both substrates (H2O2 and hemin) specifically with a Km value of 6mM and 9.33 μM respectively to form heme polymer. The heme polymer has chemical and structural properties similarities with known synthetic heme polymer (β-hematin). In the presence of H2O2, methemoglobin exhibits a spectral shift from 406nm to 417nm to form compound II. The addition of hemin substrate brings compound II (417nm) back to native enzyme (406nm) indicating hemin oxidation is a single e-oxidation process. PBN (spin trap) inhibits heme polymer formation in dose dependent manner with an IC50=25 nM further support the role of heme free radicals with heme polymerization. The inflammatory potential of heme polymer was tested for its ability to stimulate macrophage to releases ROS. J774A.1 stimulation by heme polymer causes robust ROS production within macrophage and the accumulation of large amounts of ROS in the supernatant. Surprisingly, the addition of methemoglobin along with heme polymer has pro-stimulator effects. It synergistically up-regulates several fold high ROS production and accumulation compare to their individual effects. In summary, our study highlights additional pathway of methemoglobin mediated inflammation utilizing its peroxidase activity to form heme polymer and enhance ROS production in the vicinity. Hence, our work highlights use of peroxidase inhibitors as an adjuvant therapy to reduce the patho-physiological effects during cerebral malaria.

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