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Glucose-6-phosphate dehydrogenase enzyme deficiency and its resistance to malaria

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In the pentose phosphate pathway, glucose-6-phosphate dehydrogenase (G6PD) is the key enzyme that catalyses the oxidation of glucose-6-phosphate to 6-phosphoglucono-δ-lactone and produces nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is essential for reductive biosynthesis to counter the damaging effects of oxygen, hydrogen peroxide and superoxide free radicals. These free radicals are highly reactive and unstable. They scavenge the body to seek out other electrons so that they can become a pair while damaging the cellular membranes. NADPH acts as a reductant by maintaining a reducing atmosphere which prevents oxidative damage by these free radicals. In individuals having a defective G6PD enzyme, the NADPH production is diminished and the normal detoxification of H2O2 to H2O by glutathione is inhibited. NADPH is essential for the maintenance of glutathione pools. It maintains the supply of glutathione in the cells that is used to mop up the free radicals. In the absence of G6PD, there is a decrease in the cellular detoxification of free radicals. This results in lipid peroxidation leading to the breakdown of RBC membranes and oxidation of proteins. G6PD deficiency is more severe in RBCs making them more vulnerable. The ability of RBCs to produce NADPH and glutathione is diminished which decreases the stability leading to haemolysis.

P. falciparum, the causative agent of malaria can only survive in conditions with low oxygen levels. In the hexose monophosphate shunt (HMP) pathway, RBCs survive due to the functional G6PD enzyme which produces NADPH responsible for preventing oxidative stress. However, in G6PD deficient RBCs, oxidative stress is induced. Hence, when malarial parasites are susceptible to oxidative stress, they die due to the loss of potassium from the cell. Another theory explains malarial resistance. According to this, Plasmodium falciparum oxidises NADPH and reduces the level of glutathione in erythrocytes. In the situation of G6PD deficiency, this effect becomes more severe and induces oxidative damage. Plasmodium parasites break down haemoglobin and release toxic components like iron and these substances lead to haemolysis. Hence, the development rates of Plasmodium parasites are diminished. Damaged RBCs are eliminated by the immune system via phagocytosis. This elimination decreases the growth of parasites much more during the early stages of parasites’ maturation. An antimalarial drug, primaquine is believed to act by causing oxidative stress to the parasite. Primaquine is dangerous for G6PD deficiency patients because its usage results in very severe haemolysis, but still it is the most common antimalarial drug which prevents primary parasitaemia of Plasmodium species by destroying these parasites in the liver before they reach the bloodstream and cause disease. In conclusion, the advantage of resistance to malaria balances the disadvantage of lowered resistance to oxidative damage.

Keywords: NADPH, G6PD, Haemolysis, Free radicals, Oxidative damage

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