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Immunoliposome-Mediated Drug Delivery to Plasmodium-Infected and Non-Infected Red Blood Cells as a Dual Therapeutic/Prophylactic Antimalarial Strategy

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Abstract : Bearing in mind the absence of an effective vaccine against malaria and its severe clinical manifestations causing nearly half a million deaths every year, this disease represents nowadays a major threat to life. Besides, the basic rationale followed by currently marketed antimalarial approaches is based on the administration of drugs on their own, promoting the emergence of drug-resistant parasites owing to the limitation in delivering drug payloads into the parasitized erythrocyte high enough to kill the intracellular pathogen while minimizing the risk of causing toxic side effects to the patient. Such dichotomy has been successfully addressed through the specific delivery of immunoliposome (iLP)-encapsulated antimalarials to Plasmodium falciparum-infected red blood cells (pRBCs). Unfortunately, this strategy has not progressed towards clinical applications, whereas in vitro assays rarely reach drug efficacy improvements above 10-fold. Here, we show that encapsulation efficiencies reaching >96% can be achieved for the weakly basic drugs chloroquine (CQ) and primaquine using the pH gradient active loading method in liposomes composed of neutrally charged, saturated phospholipids. Targeting antibodies are best conjugated through their primary amino groups, adjusting chemical crosslinker concentration to retain significant antigen recognition. Antigens from non-parasitized RBCs have also been considered as targets for the intracellular delivery of drugs not affecting the erythrocytic metabolism. Using this strategy, we have obtained unprecedented nanocarrier targeting to early intraerythrocytic stages of the malaria parasite for which there is a lack of specific extracellular molecular tags. Polyethylene glycol-coated liposomes conjugated with monoclonal antibodies specific for the erythrocyte surface protein glycophorin A (anti-GPA iLP) were capable of targeting 100% RBCs and pRBCs at the low concentration of 0.5 μM total lipid in the culture, with >95% of added iLPs retained into the cells. When exposed for only 15 min to P. falciparum in vitro cultures synchronized at early stages, free CQ had no significant effect over parasite viability up to 200 nM drug, whereas iLP-encapsulated 50 nM CQ completely arrested its growth. Furthermore, when assayed in vivo in P. falciparum-infected humanized mice, anti-GPA iLPs cleared the pathogen below detectable levels at a CQ dose of 0.5 mg/kg. In comparison, free CQ administered at 1.75 mg/kg was, at most, 40-fold less efficient. Our data suggest that this significant improvement in drug antimalarial efficacy is in part due to a prophylactic effect of CQ found by the pathogen in its host cell right at the very moment of invasion.

Keywords : immunoliposomal nanoparticles, malaria, prophylactic-therapeutic polyvalent activity, targeted drug delivery
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