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Adapting Tailored Nanocarriers to Evolving Antimalarial Medication Delivery Needs

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Abstract

Adapting existing antimalarial nanocarriers to novel Plasmodium stages, medicines, targeting compounds, or encapsulating structures is a method that could lead to new nanotechnology-based, low-cost malaria treatments. We investigated the modification of various liposome prototypes developed in our laboratory for the targeted delivery of antimalarial medicines to Plasmodium-infected red blood cells (pRBCs). These new models include: immunoliposome-mediated release of new lipid-based antimalarials; liposomes targeted to pRBCs with covalently linked heparin to reduce anticoagulation risks; heparin adaptation to pRBC targeting of chitosan nanoparticles; heparin use for Plasmodium stage targeting in the mosquito vector; and use of the non-anticoagulant glycosaminoglycan chondroitin 4-s.

Pre-existing antimalarial nanocarriers and targeting molecules (grey boxes) have been adjusted in their nanocapsule, targeting molecule, and drug payload to respond to novel malaria parasite therapy techniques.

Keywords: Plasmodium; Antimalarial; Nanocarriers

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Introduction

Antimalarial medications have the capacity to target a variety of disease life stages within two distinct hosts: people and insect vectors. While taking a blood meal, a parasitized female Anopheles mosquito inoculates sporozoites of the malaria parasite, the protist Plasmodium spp., into a person. Sporozoites enter hepatocytes after migrating through the epidermis and circulation to the liver. Sporozoites mature into merozoites, which enter the circulation, invade red blood cells (RBCs), and multiply asexually to produce daughter cells that infiltrate new RBCs, thus perpetuating the blood-stage cycle that progresses through the ring, trophozoite, and schizont stages. Some parasites eventually develop sexual stages, female and male gametocytes, which a mosquito consumes from peripheral blood. Micro- and macrogametocytes mature into male and female gametes when infected bloodmeal reaches the insect's midgut. After fertilisation, the zygote develops into an ookinete, which passes through the midgut epithelium and becomes an oocyst, which releases sporozoites. When sporozoites move to the salivary glands and are injected into a human by the next mosquito bite, the malaria transmission cycle is repeated. With malaria elimination now firmly on the global research agenda, but resistance to currently available treatments on the rise, there is an urgent need to invest in research and development of new therapeutic options [1-5]. Encapsulation of pharmaceuticals in targeted nanovectors is a rapidly emerging area with clear application to infectious disease treatment, and pharmaceutical nanotechnology has been highlighted as a potentially vital tool in the future fight against malaria. Nanoparticle-based targeted delivery approaches may play an important role in the treatment of malaria because they may allow for low overall doses that limit the toxicity of the drug for the patient, administration of sufficiently high local amounts to minimise the evolution of resistant parasite strains, improvement of the efficacy of currently used hydrophilic (low membrane trespassing capacity) and lipophilic antimalarials (poor aqueous solubility), and use of orpha Because of the adaptability of nanovectors, it is possible to assemble various parts to create chimeric nanovessels adapted to the needs of alternative administration routes, specific intracellular targets, or drug combinations. The nanovector design is adaptable to other targets, such as different Plasmodium species or infected cells other than the erythrocyte, by modifying its component parts. The targeting of the transmission stages that allow parasite transfer from human to mosquito and vice versa, which reflect the pathogen's weakest points in its life cycle, is of special relevance here. During the primary stage of malaria infection in the liver,

heparin and HS are targets for the circumsporozoite protein in sporozoite attachment to hepatocytes [6]. CS proteoglycans in the mosquito midgut and synthetic CS mimics have been shown to bind Plasmodium ookinetes as a crucial step in host epithelial cell invasion, whereas ookinete-secreted proteins have substantial affinity to heparin. Because these cells lack endocytic mechanisms, a rather fluid liposome lipid bilayer is necessary to favour fusion events with the pRBC plasma membrane. As a result, these liposomes are leaky for tiny pharmaceuticals encapsulated in their lumen, and when membrane fusion occurs, only a small fraction of the previously contained medication is transported into the cell. Liposomes constructed of saturated lipids, on the other hand, have less fluid bilayers that retain medications with high efficacy, while fusion events with pRBC membranes are considerably reduced, which may also lower the amount of luminal cargo delivered to the target cell [7].

Formation of Liposomes

The antimalarial medication primaquine (PQ) was encapsulated in DOTAP-containing liposomes by dissolving it at 1.2 mM in the PBS buffer used to hydrate the lipids and removing non-encapsulated drug via ultracentrifugation. To crosslink the amine groups in the liposomes with the carboxyl groups of heparin (sodium salt from porcine intestinal mucosa, 13 kDa mean molecular mass) or its hexa- and octasaccharide fragments, the polymers were first dissolved at 1 mg/mL in MES activation buffer (ethane sulfonic acid, 0.5 M NaCl, pH 5.0). The activated heparin solution was treated with 2 mM N-N'-ethylcarbodiimide hydrochloride and 5 mM N-hydroxysuccinimide. Liposomes were ultracentrifuged and dissolved in 10 pellet volumes of PBS immediately before being added to pRBC cells with a further cafold dilution to eliminate unbound heparin. Liposomes were lipid extracted for measurement of contained PQ. In brief, the liposome pellet was treated with methanol:chloroform:0.1 M HCl after ultracentrifugation, and the PQ content in the upper water-methanol phase was evaluated by measuring A320 against a calibration curve of known PQ concentrations after phase separation. Heparin-containing liposomes were tested for coagulation in vitro, as previously described. The concentration of heparin was measured using the Alcian Blue technique [8,9].

Chitosan Nanoparticle Polymerization [10]

Chitosan nanoparticles were created using a coacervation process previously described. In a nutshell, 0.5 g chitosan was dissolved in 50 mL of an aqueous solution of 2% v/v acetic acid and 1% w/v Pluronic F-68. To create a suspension of chitosan nanoparticles, 12.5 mL of a 20% w/v sodium sulphate solution was added dropwise to the chitosan solution and mechanically stirred for 1 hour. The colloidal solution was then cleaned using multiple cycles of centrifugation and re-dispersion in water until the conductivity of the supernatant reached 10 S/cm. Following standard techniques, isothermal titration calorimetry measurements were taken using a VP-ITC microcalorimeter. 16 Chitosan nanoparticles and heparin tagged with fluorescein isothiocyanate were mixed 10:1 w/w and incubated for 90 minutes with mild orbital mixing to determine fluorescence. Following a centrifuge step to remove unbound heparin, the pellet was placed in PBS, its fluorescence was measured, and the associated concentration was calculated using a standard linear regression of known FITC concentrations. The fluorescence of the supernatant was also examined to confirm that it contained the percentage of heparin that was not linked with the nanoparticles.

Spectroscopy of Force

For fluorescent labelling of CSA, fluorescence confocal microscopy 16, and cryo-transmission electron microscopy sample imaging, existing procedures were employed. The Supplementary Materials contain more information on these strategies. Binding forces between CSA and pRBCs infected with the P. falciparum CS2 strain were evaluated using an atomic force microscope (AFM) and single-molecule force spectroscopy (SMFS), as previously described. Data are reported as the mean standard deviation of at least three independent experiments, and the accompanying standard deviations in histograms are represented by error bars. The parametric When the data had a Gaussian distribution, the Student's t test was employed to compare two independent groups, and differences were considered significant when P 0.05. IC50 values were computed by nonlinear regression with an inhibitory dose-response model using GraphPad Prism5 software. For linear regression, concentrations were transformed using the natural log, and regression models were adjusted for the assayed duplicates. This antiparasitic impact suggested that lipids entered the cell and reached the pathogen as a result of random interactions of liposomes with pRBCs. We conducted confocal fluorescence microscopy analysis of pRBC-targeted immunoliposomes containing 7% of the rhodamine-tagged lipid DOPE-Rho in their formulation to determine whether such process occurred through whole liposome entry or was mediated by transfer phenomena between the apposed lipid bilayers of liposomes and pRBCs. As previously described23, specific pRBC targeting was achieved by functionalizing the liposomes with the monoclonal antibody BM1234 produced against the membrane-associated histidine-rich protein expressed by P. falciparum. Heparin's dual activity as an antimalarial medication and as a pRBC targeting component has been offered as a viable new option for future malaria therapeutics. Existing models, on the other hand, contain electrostatically attached heparin, which is prone to peeling off liposome surfaces while in the bloodstream, posing a danger of anticoagulation and internal bleeding. To investigate potential mitigation measures, we modified our earlier design to include covalently bonded heparin on primaquine (PQ)-loaded liposomes. PQ was chosen for its high IC50 for in vitro P. falciparum growth, which allowed for quick and straightforward sample concentration assessment, as well as for reasons related to current antimalarial chemotherapeutic demands. Given the endogenous nature of chitosan in these animals and the projected imperviousness of mosquitoes to the presence of blood anticlotting medicines, the simple binding of heparin to chitosan leads in nanoparticles that are believed to be harmless for insects. This prompted us to investigate the ability of heparin to target Plasmodium stages in Anopheles. Fluorescently tagged heparin-FITC was found to bind solely to

Plasmodium gametocytes, ookinetes, oocysts, or sporozoites when added to solutions containing Plasmodium gametocytes, ookinetes, oocysts, or sporozoites. AFM force spectroscopy was used to investigate the adhesion between pRBCs infected with the CSA-binding P. falciparum FCR3-CSA strain and Chinese hamster ovary cells expressing CSA on their surface, generating a mean rupture force of pN, identical to that found here using isolated CSA. Because CSA interaction with pRBCs has been reported as occurring via binding to PfEMP1 on erythrocyte surfaces, the adhesive force between the two cell types was previously attributed exclusively to the CSA-PfEMP1 relationship. The inclusion of 500 g CSA/mL in solution did not limit the binding of CSA on the AFM cantilever to pRBCs, whereas 100 g CSA/mL dramatically hindered pRBC-CHO adhesion.

Discussion

Despite a lack of commercial incentives for research in nanomedicine applications to malaria, a variety of liposome- and polymer-based nanocarriers designed for targeted antimalarial drug delivery have been produced. Although effective efforts have been made to create novel nanostructures with cheap synthesis costs while still demonstrating good performance in lowering medication IC50, new ways are necessary to better optimise these limited resources. Implementing novel delivery methods is less expensive than discovering new antimalarial medications, and it has the potential to increase the rate of release of current and future molecules. The three components of a targeted therapeutic nanovector can be swapped out like Lego blocks to create new structures that are more suited to each situation. The data presented here allow us to propose several combinations of nanovector parts that could be adapted to new antimalarial strategies: liposomes formulated with antimalarial lipids and targeted with covalently bound heparin could carry the active agents in their bilayer membranes with little leaking before reaching their target site and with low hemorrhagic risk. Although liposomes are insufficient for the oral formulations currently required to treat malaria in endemic areas, intravenous drug administration may be a useful approach in a future eradication scenario in which the last cases caused by hyper-resistant parasite strains will be treatable with sophisticated, targeted liposomal nanocarriers. Liposomes have a long history of established biocompatibility, and their lipid formulation can be tailored to provide either fast or gradual drug release, making them suitable for transporting antimalarial medicines with a variety of pharmacokinetic profiles. Because Plasmodium resistance to heparin has yet to be demonstrated, heparin-based targeting will almost certainly be more long-lasting than pRBC recognition based on antibodies, which are typically raised against highly variable exposed antigens whose expression is constantly modified by successive parasite generations. The particular binding of CSA to pRBCs infected by the P. falciparum CS2 strain, which sequesters in the maternal circulation of the placenta, implies that future nanovectors functionalized with CSA could be tailored to target medicines to pRBCs for the treatment of placental malaria.

Conclusion

As removing an insect species may cause unforeseen perturbations in ecosystems with potentially negative side effects (e.g. crop failure if pollinators are accidentally harmed), mosquito-friendly antimalarial techniques should be preferred whenever possible. Thus, administering medications to mosquitos to rid them of malaria with the goal of preventing disease transmission is a viable option worth considering.

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