Synthetic Antimalarial Peptides to Combat Drug Resistance in Malaria

ShT-05.2-1

E. Kiper *[I], D. Ben Hur *[I], D. Alfandari [I], N. Wani[I], N. Zaharoni [I], I. Rosenhek-Goldian [II], Z. Porat [III], M. Goldsmith[I], Y. Shai[I], N. Regev-Rudzki[I]

[I]Faculty of Biochemistry, Department of Biomolecular Sciences, Weizmann Institute of Science, Rehovot, Israel, [II]Department of Chemical Research Support, Weizmann Institute of Science, Rehovot, Israel, [III]Department of Life Sciences Core Facilities, Weizmann Institute of Science, Rehovot, Israel

Malaria is a deadly infectious disease caused by the *Plasmodium falciparum* (*Pf*) parasite, the most virulent *Plasmodium* species. The lack of an effective vaccine and the emergence of drug-resistant parasites increase the challenge of eradicating malaria worldwide. Antimicrobial peptides (AMPs) offer a promising therapeutic avenue for developing new treatments based on their broad activity against the membranes of pathogens. Here, we identified a set of synthetic AMPs capable of inhibiting *Pf* proliferation while the parasite is growing within its host human red blood cells (RBCs). Importantly, these AMPs exhibit a non-toxic effect on uninfected human RBCs. Fluorophore-tagged AMP demonstrated stronger binding affinity to the infected RBCs (*Pf*-iRBCs) in contrast to uninfected ones. We subsequently employed atomic force microscopy to investigate the mode of action of these peptides. We revealed mechanical alterations in the plasma membrane of the treated *Pf*-RBCs, indicating the presence of a distinct membranal factor that mediates the peptide interaction. To further identify the key components involved in the AMP-membrane interaction, we used unilamellar liposomes to model the plasma membrane of *Pf*-iRBCs versus uninfected RBCs and measured the peptide binding. Remarkably, we found that the presence of cholesterol in the RBC membrane inhibits the peptide binding, whereas its absence, as in *Pf*-iRBCs' membranes, enhances its activity. Overall, our data show that synthetic AMPs could serve as new antimalarial drugs, capitalizing on the membrane alterations induced by the parasite during its blood stage. Furthermore, the broad mode of action of these AMPs may reduce the likelihood of drug resistance.

* The authors marked with an asterisk equally contributed to the work.