A structural clue to attacking malaria's 'Achilles heel'

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Credit: National Cancer Institute

Researchers from The Scripps Research Institute (TSRI) and PATH's Malaria Vaccine Initiative (MVI) have shed light on how the human immune system recognizes the malaria parasite though investigation of antibodies generated from the RTS,S malaria vaccine—work that could boost the development of a more potent vaccine against the global killer.

In a study published this week in the journal *Proceedings of the National Academy of Sciences*, the researchers provide an atomic-level view of how human antibodies bind to an important malarial surface protein, the circumsporozoite protein (CSP), to protect against the malaria parasite. These new structures could potentially help scientists enhance RTS,S efficacy and duration, the world's most advanced malaria vaccine to date, which has shown partial protection against the disease in a large-scale Phase 3 clinical trial.

The RTS,S vaccine was the outcome of a long-standing collaboration between PATH and GSK that began in 2001 and involved research institutions in Africa and worldwide. RTS,S is the first and, to date, the only vaccine to show a protective effect against malaria among young children in Phase 3 clinical trials.

Efforts continue to enhance the vaccine's efficacy and duration of protection against malaria, a major public health problem that infects millions of people each year. An estimated 429,000 people died from the mosquito-borne illness in 2015 and 212 million people were infected.

Characterizing a key site of vulnerability on the malaria parasite

In this study, the investigators structurally characterized antibodies to CSP produced in response to a delayed fractional dose trial (MAL071) of the RTS,S-vaccine. Ian Wilson, D.Sc., Hansen Professor of Structural Biology at TSRI, led the study. David Oyen, Ph.D., a research associate in Wilson's lab, is the first author. The antibodies were discovered from the protected vaccines by scientists at Atreca, a biotech company that worked in the collaboration.

"In order to design a next-generation vaccine, you need to know first the atomic details of highly protective antibody interaction," said Oyen. "Specifically, you need to know what part of the elicited antibodies recognizes what part of the malaria antigen."

"What Oyen and Wilson have done, together with the other collaborators, is to give us a very detailed picture of how those antibodies do the business of rejecting the (malaria) parasite, and that's very important," said Rick King, Ph.D., MVI's director of research and development and a co-author on the study. "This information will be very useful as we work to modify the existing vaccine so that it can be more protective."

In their study, Wilson and colleagues used X-ray crystallography and other sophisticated imaging technologies to analyze how two functional antibodies from RTS,S-vaccinated individuals latched onto the CSP protein target.

TSRI Professor Andrew Ward, Ph.D., a co-author whose lab provided electron microscopy expertise, said the researchers created structural images of the antibody binding to determine the precise area the immune system goes after.

"We were looking at what piece of the (CSP) protein the antibody is targeting," Ward said. "If we can focus the immune response on the real Achilles heel, the sites of vulnerability on the CSP protein, we would hope to get a more effective vaccine response."

The researchers drilled down to how the antibodies recognized the immunodominant NANP repeats within CSP, considered the area most important for eliciting a strong immune response and the basis for the RTS,S vaccine.

The research team pinpointed the number of NANP repeats that interacted with the two antibody fragments and established how the antibodies bind to the NANP repeat region.

"We found that these antibodies bind certain elements of the repeat peptides in a similar way," said Wilson, noting this information could be useful in engineering a next-generation vaccine. "The goal is to direct the immune system towards a particular region of the malaria pathogen surface protein to produce the type of antibodies that you know are or have a good possibility of being protective."

With this new structural map, the scientists have a better understanding of where the vaccine needs to be stabilized to better mimic CSP and "teach" the immune system to target malaria.

More information: David Oyen et al. Structural basis for antibody recognition of the NANP repeats in Plasmodium falciparumcircumsporozoite protein, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1715812114

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