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A Challenge for the Development of Malaria Vaccines: Polymorphic Target Antigens

Colin Sutherland

Parasites of the genus *Plasmodium* cause many hundreds of millions of cases of malaria worldwide every year. There is recently renewed optimism that in the future effective vaccination will join the current strategies of preventive and therapeutic uses of antimalarials, and of reduction in human-vector contact, as part of the global malaria control toolkit.

Malaria vaccine targets

The complex life cycle of the malaria parasite, a protozoan of the phylum Apicomplexa, requires a sophisticated array of proteins. These are encoded by a genome of 23 Mb distributed across 14 chromosomes in *P. falciparum* [1], significantly larger than the genome of any human pathogen for which effective vaccines have been successfully developed. Vaccine candidates for *P. falciparum* and *P. vivax* that have advanced to clinical trials in recent years are targeted against two distinct stages of the parasite life cycle. The first is the sporozoite, which is injected by the bite of a mosquito into the human host as a haploid, free-living unicellular form, and which seeks out the liver, where it invades a hepatocyte and undergoes intracellular multiplication. Among key target antigens at this stage are thrombospondin-related adhesive protein (TRAP), liver-stage antigen 1 (LSA-1) and circumsporozoite protein (CSP). The most successful malaria vaccine to date, the recombinant protein RTS,S administered with the adjuvant AS02A, afforded sustained protection to ~30% of children under five years of age in a large proof-of-principle Phase II trial in Mozambique [2]. This vaccine is based on the CSP antigen, and is designed to prevent infection.

A second major class of malaria vaccines targets the blood stage of the life cycle. This intraerythrocytic stage of infection is responsible for the syndrome of clinical symptoms familiar to us as malaria. Free-living merozoites invade the blood, before invading a host erythrocyte, present the immune system with a number of potential immunogens. Among these, merozoite surface protein 1 (MSP-1) is considered one of the most promising vaccine targets, and a number of candidate MSP-1 vaccines are currently in the development pipeline. Many of these are based on the 19 kDa polypeptide at the carboxyl terminus of the MSP-1 protein, MSP-119. As a prime target of natural immune responses in malaria-exposed populations, MSP-1 is a polymorphic antigen, and many variants can occur in a single parasite population. Therefore, there is a risk that MSP-1 vaccine-elicited immune responses may be variant specific, and thus not provide protection against all parasite genotypes encountered within a given population. The MSP-119 portion of the molecule is relatively conserved, but does contain six polymorphic amino acid residues that may contribute to immune evasion by the parasite.

Developing the Capacity for Malaria Vaccine Trials—Bandiagara, Mali

Renewed interest in the testing of malaria vaccines at a number of clinical trial sites in sub-Saharan Africa has lead to development of the infrastructure and expertise required for Phase II and Phase III studies of vaccine safety, immunogenicity, and efficacy. One of these sites is at Bandiagara, Mali, where malaria transmission is intense but highly seasonal. In this month’s *PLoS Medicine*, Shannon Takala and colleagues present a detailed longitudinal analysis of polymorphisms in the *msp-1* genes of parasite isolates taken from a cohort of a broad age range.
be significantly more common in two other haplotypes, appeared to the 3D7 haplotype ETSSRL, and in this population. Interestingly, haplotypes might be more effective or both of the more prevalent specific, a vaccine targeting either combinations needs to be covered by a vaccine in order to counteract the effect of polymorphism at these residues.

Gathering Intelligence

The data presented by Takkala et al., gathered in the absence of any intervention with a vaccine, demonstrate the potential impact that parasite population diversity could have on the outcome of MSP-19 vaccine trials. Confirmation in other endemic settings is required to verify the evidence that certain residues in this antigen may be particularly important in eliciting sequence-specific protection, and that particular haplotypes are associated with lower parasite densities. Nevertheless, this study provides ample warning that analysis of antigen diversity in the target parasite population should not only be gathered as part of postintervention evaluation in vaccine trials [4], but should be part of the intelligence gathering undertaken when planning intervention studies in the first place.

Acknowledgments

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References

1. Gardner MJ, Hall N, Fung E, White O, Berriman M, et al. (2002) Genome sequence of the human malaria parasite Plasmodium falciparum. Nature 419: 498–511.
2. Alonso PL, Sacarlal J, Aponte JJ, Leach A, Macete E, et al. (2005) Duration of protection with RTS,S/AS02A malaria vaccine in prevention of Plasmodium falciparum disease in Mozambican children: Single-blind extended follow-up of a randomised controlled trial. Lancet 366: 2012–2018.
3. Takala SL, Costibaly D, Thera MA, Dicko A, Smith DL, et al. (2007) Dynamics of polymorphism in a malaria vaccine antigen at a vaccine-testing site in Mali. PLoS Med 4: e93. doi:10.1371/journal.pmed.0040093
4. Enosse S, Dobano C, Quelhas D, Aponte JJ, Lievens M, et al. (2006) RTS,S/AS02A malaria vaccine does not induce parasite CSP T cell epitope selection and reduces multiplicity of infection. PLoS Clin Trials 1: e5. doi:10.1371/journal.pctr.0010005