Malaria

The merozoite surface protein-1 (MSP-1) is a primary vaccine candidate antigen. Study of allelic diversity in *Plasmodium falciparum* revealed extensive variation in distribution of MSP-1 variants in the Amazon Basin, with examples of epidemic expansion of clones carrying MSP-1 haplotypes. Occurrence of variant-specific antibodies and the differential profile of IgG subclass antibody recognition of different regions of MSP-1 were revealed by serological studies using MSP-1-derived recombinant peptides. These results have major implications for malaria vaccine development and the molecular evolution of MSP-1.

Patterns of allelic variation in the malaria vaccine candidate merozoite surface protein-1 (MSP-1) from field isolates of *Plasmodium falciparum,* collected over a period of 14 years from several sites in the Amazon region of Brazil, were investigated in the most extensive study of MSP-1 allelic diversity outside Africa, the only such study done in a hypoendemic region.

Extensive temporal and spatial variation in the distribution of msp-1 variants was found across the Amazon Basin. Sequence micro-heterogeneity in the 5´ region of the msp-1 gene, which codes for the C-terminal vaccine-candidate peptide MSP-119, was characterized in 130 isolates collected in Rondônia, with two previously unknown MSP-119 haplotypes also being identified. Contrasting with previous work in Africa, a strong linkage disequilibrium between polymorphic sites >1 kb apart within the 5-kb msp-1 gene was seen, indicating that effective rates of meiotic recombination at this locus are quite variable. Moreover, two instances of epidemic expansion of clones carrying particular msp-1 haplotypes were characterized. Sequence diversity in the most variable region of msp-1, the repetitive block 2, was also characterised in 59 isolates. Insertions and deletions of repeat units in block 2 (that may result from illegitimate [mitotic] recombination) generated several new msp-1 alleles, but retained significant linkage disequilibrium between polymorphisms located in the non-repetitive regions flanking the repeat array. Variation patterns in non-repetitive block 4 were consistent with gene conversion events. These results indicate a role for non-reciprocal (non-meiotic) exchanges in creating sequence variation in this antigen in natural parasite populations.

Patterns of naturally-acquired antibody responses to MSP-1 were examined in semi-immune or non-immune Brazilian patients with malaria and clinically immune subjects from Senegal, using recombinant peptides representing conserved (blocks 3 and 17), dimorphic (block 6) and polymorphic (block 2) regions of the antigen. Contrasting patterns of IgG subclass response to different regions of MSP-1 were observed, as well as the presence of variant-specific antibodies to block 2. As a rule, antibodies recognized mostly variable regions of this antigen. These results suggest that insertions and deletions of repeat motifs in block 2 may represent a strategy of immune evasion, with implications for the use of MSP-1-derived peptides in malaria vaccines, since new variants generated by either mitotic or meiotic recombination events within repeat arrays may be favored by immune-mediated selection of mutants. ■

References:

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Merozoite surface protein-1 of Plasmodium falciparum*: allelic diversity and antibody recognition in the Brazilian Amazon*

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