DNA secondary structures are associated with recombination in major Plasmodium falciparum variable surface antigen gene families - DTU Orbit (16/12/2018)

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Many bacterial, viral and parasitic pathogens undergo antigenic variation to counter host immune defense mechanisms. In Plasmodium falciparum, the most lethal of human malaria parasites, switching of var gene expression results in alternating expression of the adhesion proteins of the Plasmodium falciparum-erythrocyte membrane protein 1 class on the infected erythrocyte surface. Recombination clearly generates var diversity, but the nature and control of the genetic exchanges involved remain unclear. By experimental and bioinformatic identification of recombination events and genome-wide recombination hotspots in var genes, we show that during the parasite’s sexual stages, ectopic recombination between isogenous var paralogs occurs near low folding free energy DNA 50-mers and that these sequences are heavily concentrated at the boundaries of regions encoding individual Plasmodium falciparum-erythrocyte membrane protein 1 structural domains. The recombigenic potential of these 50-mers is not parasite-specific because these sequences also induce recombination when transferred to the yeast Saccharomyces cerevisiae. Genetic cross data suggest that DNA secondary structures (DSS) act as inducers of recombination during DNA replication in P. falciparum sexual stages, and that these DSS-regulated genetic exchanges generate functional and diverse P. falciparum adhesion antigens. DSS-induced recombination may represent a common mechanism for optimizing the evolvability of virulence gene families in pathogens.

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