In silico identification of genetically attenuated vaccine candidate genes for *Plasmodium* liver stage

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In silico identification of genetically attenuated vaccine candidate genes for *Plasmodium* liver stage

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Abstract

Genetically attenuated parasites (GAPs) that lack genes essential for the liver stage of the malaria parasite, and therefore cause developmental arrest, have been developed as live vaccines in rodent malaria models and recently been tested in humans. The genes targeted for elimination were often identified by trial and error. Here we present a systematic gene—protein and transcript—expression analyses of several *Plasmodium* species with the aim to identify candidate genes for the generation of novel GAPs. With a lack of liver stage expression data for human malaria parasites, we used data available for liver stage development of *Plasmodium yoelii*, a rodent malaria model, to identify proteins expressed in liver stage but absent from blood stage parasites. An orthology-based search was then employed to identify orthologous proteins in the human malaria parasite *Plasmodium falciparum* resulting in a total of 310 genesexpressed in liver stage but lacking evidence of protein expression in blood stage parasites. Among these 310 possible GAP candidates, we further studied *Plasmodium* liver stage proteins by phyletic distribution and functional domain analyses and shortlisted twenty GAP-candidates: these are *fabB*/F, *fabI*, *arp*, 3 genes encoding subunits of the PDH complex, *dnaJ*, *urm1*, *rS5*, *ancp*, *mcp*, *arh*, *gk*, *lisp2*, *valS*, *palm*, and four conserved *Plasmodium* proteins of unknown function. We believe that parasites lacking one or several of these genes can yield new attenuated malaria parasites for experimental vaccination studies.