Commentary

Identifying an essential interaction between malaria parasites and erythrocytes unlocks the door to promising vaccine targets

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Invited Commentary on key findings in the literature

It has long been known that erythrocyte invasion by the merozoite stage of the malaria parasite is a specific receptor-mediated process. Over the last twenty years several laboratories have attempted to exploit novel molecular and biochemical approaches to identify the surface molecules on both the parasite and erythrocyte membranes that mediate erythrocyte invasion. Research has focused on two groups of proteins secreted from the rhoptries and micronemes, secretory organelles that, upon contact with the host cell, release proteins essential both for orientation of the parasite at the erythrocyte surface and for invasion and formation of the parasitophorous vacuole. A number of ligand:receptor interactions have been identified yet attempts to disrupt these interactions experimentally with specific antibodies or through competitive binding assays have shown an inhibitory effect only in a subset of parasite strains.¹ Similarly, genetic knockouts of these parasite ligands have failed to completely block parasite invasion of erythrocytes because of the functional redundancy of different receptor-ligand pairs.

Furthermore, many parasite ligands have a low affinity for their corresponding erythrocyte receptors yet achieve high overall avidity due to high density of both the receptors and ligands on the parasite and erythrocyte surfaces at the point of contact. Therefore, many biologically relevant parasite-erythrocyte interactions cannot be investigated using conventional biochemical assays such as co-immunoprecipitation because they are designed to reveal high affinity interactions. In a recent paper by Crosnier *et al.*² a novel screen was employed to detect low-affinity protein interactions between PfRh5 (Reticulocyte-binding protein homologue 5), a gene previously shown to be essential for erythrocyte invasion,³ and a panel of all the surface-exposed protein domains putatively expressed on the erythrocyte. To detect biochemically a low affinity, high avidity interaction, the authors used a mammalian cell expression system to produce pentamers of candidate erythrocyte protein domains and checked for *in vitro*

binding. A single protein was implicated by this screen, basigin, a member of the immunoglobulin superfamily that determines the Ok blood group antigen.⁴

The requirement for the interaction between PfRh5 and basigin in erythrocyte invasion was confirmed through several lines of experimental evidence: excess soluble basigin, anti-basigin antibodies and knock-down by RNAi all led to a drastic reduction in erythrocyte invasion by merozoites. Importantly, a similar effect was seen across all parasite strains tested, including several laboratory-adapted lines and six freshly isolated parasite isolates from the field in West Africa. If this interaction is so conserved and fundamental we might expect selection for mutations in basigin in malaria-endemic areas that diminish parasite binding. The authors assayed existing genetic basigin variants, some of which showed reduced binding affinity for PfRh5. None of these were isolated from malaria-endemic areas, however, and future studies will assess whether in malaria-endemic regions basigin gene variants are causally associated with malaria incidence. One glaring question that emerges from this research is whether the inhibitory effect on invasion mediated by antibodies against a (presumably) continually exposed erythrocyte antigen is mimicked by antibodies against the parasite antigen PfRh5, which might only be exposed fleetingly following release from the rhoptry on contact with the erythrocyte. In this light, very recent work showing that vaccine-induced anti-PfRH5 antibodies can potentially inhibit parasite invasion *in vitro*⁵ is very encouraging and suggests that future malaria vaccine research will focus heavily on this basigin-PfRH5 interaction.

References

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