Placental malaria and circumsporozoite protein-specific immunity

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Abstract

Circumsporozoite protein-specific active and passive immunization can protect significantly against *Plasmodium falciparum* malaria and are being considered as tools to prevent placental malaria. Despite recent encouraging findings, a closer view of the underlying biology indicates significant challenges to preventing placental malaria.

Plasmodium falciparum malaria and acquisition of protective immunity

Malaria continues to claim hundreds of thousands of lives each year, mainly among young African children. The reason that they bear the brunt of the burden is that survivors develop substantial clinical immunity over the first decade of life. Severe malaria is therefore rare among adults in areas with stable transmission of *P. falciparum* parasites. The protection afforded is mediated by IgG antibodies that recognize the asexual blood stages and limit their multiplication (anti-disease immunity), often to very low, even sub-microscopic, levels [1]. In contrast, acquisition of anti-infection immunity, which relies on destruction of the pre-erythrocytic stages that precede the asexual blood stages, does not seem to play a major role [2]. Clinically immune adults therefore often carry low-level parasitemia for extended periods. Despite the above, durable and sterilizing immunity to the pre-erythrocytic *P. falciparum* parasites can be induced under the right circumstances [3]. The circumsporozoite protein (CSP) covers the sporozoites that are injected by blood-feeding mosquitoes to initiate the infection. CSP is the main target of pre-erythrocytic immunity and has been the main antigen focus of malaria vaccine development right from the beginning. Encouraging recent studies provide strong evidence that CSP-specific IgG can protect significantly against infection with *P. falciparum* parasites, whether the antibodies are acquired in response to subunit vaccination or provided by passive immunization [4,5]. Accordingly, two CSP-based vaccines have been approved by the World Health Organization and are starting to be rolled out among African infants.

Placental malaria

Although *P. falciparum* malaria is mainly a severe health problem among young children in Africa, it has long been realized that women become highly susceptible to placental malaria (PM) when they become pregnant, particularly for the first time. PM is the result of selective

accumulation of infected erythrocytes (IEs) in the intervillous space, where it can cause placental inflammation and adverse pregnancy outcomes [6].

The non-sterile but clinically very significant immunity acquired in childhood and adolescence does not protect against PM. There are several reasons for that. One is that the placental IE sequestration is mediated by a parasite-encoded antigen, VAR2CSA, that is antigenically distinct from all other *P. falciparum* proteins, including the other members of the PfEMP1 antigen family to which it belongs [7]. The PfEMP1 adhesins are expressed on the IE surface, where they enable IE adhesion to host vascular receptors (sequestration) to avoid splenic destruction. Importantly, different PfEMP1 bind to different host receptors, and the parasites can switch expression among them to evade PfEMP1-specific immunity. As expression of these receptors varies markedly among tissues and organs, the expressed PfEMP1 is an important determinant of clinical presentation of malaria [7]. Another, equally important, reason for the PM susceptibility of primigravidae is that VAR2CSA binds exclusively to a placenta-restricted receptor, and VAR2CSA expression is therefore only compatible with parasite survival in a pregnant host. As a result, children, men, and women who have never been pregnant do not possess significant VAR2CSA-specific IgG.

These features combine to make primigravidae exquisitely susceptible to PM. As soon as the placenta forms and the new receptor becomes available early in the first trimester, parasites that switch to expressing VAR2CSA gain a huge survival advantage. Importantly, this susceptibility to PM is independent of pre-existing protective immunity to other types of *P. falciparum* malaria. It gradually disappears over successive *P. falciparum*-exposed pregnancies, as protective VAR2CSA-specific immunity is acquired.

Circumsporozoite protein-specific immunization as a tool to prevent placental malaria

Current evidence indicates that CSP-specific immunity wanes rapidly, but with timely intervention it may be sufficient to cover the critical period early in life, when protective

immunity against *P. falciparum* malaria is normally acquired. Indeed, the main target population of current CSP-based vaccines is infants. However, the duration of CSP-specific protection among adults either vaccinated or passively immunized with monoclonal antibody is sufficient to suggest that these interventions may also be useful as much-needed tools to prevent PM [4,5]. Although this may appear attractive, there are several caveats that should be borne in mind. First, PM causes damage from very early on in pregnancy [8], and protection should therefore be in place as near conception as possible. Early post-conception intervention is complicated by the fact that anti-malarial chemotherapy options are very limited at that time (see below) and because only about a third of African women have their first antenatal care contact in the first trimester [9]. Three doses of vaccine at the four-weekly intervals are required for optimal protection, delaying onset of benefit, while monoclonal antibodies may not exert protection beyond six months, only covering part of pregnancy [5]. On the other hand, pre-conception intervention is complicated by the obvious problem of timing, unless the longevity of protective levels of the CSP-specific IgG can be dramatically improved. It seems likely that regular re-immunization of all women of child-bearing age will be required. High protective efficacy of the intervention is necessary as sporozoites that survive can proceed unhindered to cause PM in the absence of VAR2CSA-specific immunity. Another complication relates to the fact that while CSP-specific immunity can protect against new infections, it has no impact on infections that already exist, and as alluded to above, clinically immune individuals can harbor low-grade parasitemia in the absence of any symptoms. Although the evidence is sporadic, it appears that such silent infections can persist at least for several years [10]. Rather than being the result of new infections acquired during pregnancy, PM is often precipitated by such “Trojan horses” [11]. Radical cure of existing infections is thus a prerequisite at the time of CSP-specific immunization, and it was indeed implemented in the study by Diawara *et al.* [4].

Concluding remarks

Even if CSP-based immunization – active or passive – could completely prevent new infections, timing it optimally will be difficult. Clearance of pre-existing asexual infections by chemotherapy will be required. It seems likely that regularly repeated immunization will also be necessary. Overall, this strategy may thus be neither practical nor cost beneficial. Although VAR2CSA-specific vaccination would seem an obvious alternative approach, the trials conducted so far did not yield the expected cross-reactive and IE adhesion-blocking antibodies. This major disappointment is compounded by recently discovered apparent differences in the protective effector functions of IgG acquired in response to PM versus antibodies induced by vaccination [12]. To sum it up, PM is a more intractable problem than is often assumed.

Declaration of interests

The authors declare no competing financial interests. LH is a member of the Trends in Parasitology advisory board.

Authorship contribution statement

All authors contributed to the manuscript, agree to the Journal's publication policies, and approved its contents prior to submission.

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