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Epstein-Barr virus, malaria and endemic Burkitt lymphoma

Thirumalaisamy P. Velavan

[a] Institute of Tropical Medicine, Universitätsklinikum Tübingen, Tübingen, Germany
[b] Vietnamese- German Center for Medical Research (VGCARE), Hanoi, Viet Nam
[c] Fondation Congolaise pour la Recherche Médicale (FCRM), Brazzaville, Congo
[d] Faculty of Medicine, Duy Tan University, Da Nang, Viet Nam

Plasmodium falciparum, the causative agent of severe malaria, is itself not considered a carcinogenic organism. However, the occurrence of endemic Burkitt lymphoma (eBL; first described in 1958 by Dennis Burkitt in Uganda) in tropical Africa is apparently associated with intense and repeated exposure to *P. falciparum* infections. Concurrent infection with *P. falciparum* malaria and Epstein-Barr virus (EBV) is regarded the main risk factor for the development of eBL. The precise mechanisms of how interactions of these two pathogens induce eBL pathogenesis have, however, been an unsolved mystery for decades.

In an article in the present issue of *EBioMedicine*, Derkach and colleagues have assessed antibody reactivity to 13 *P. falciparum* erythrocyte membrane protein 1 (*Pf*EMP1) and 3 non-*Pf*EMP1 antigens, (potential targets of acquired immune responses, in two sex-age matched study cohorts from Ghana (150 eBL cases and 150 controls) and Uganda (194 eBL cases and 600 controls) (Derkach et al. [1]). Lower IgG reactivity to *Pf*EMP1 antigens in eBL cases compared to controls was observed. In addition, the study calls attention to the salient role of the cysteine-rich interdomain region α1 (CIDRα1) in the pathophysiology of malaria and the predisposition to attenuated humoral immunity, contributing to the frequent occurrence of eBL in tropical Africa where *P. falciparum* malaria is holoendemic.

The study showed that IgG reactivity to the CIDRα1 domains, which are associated with severe malaria, was stronger than to other CIDR domains in cases and controls, and that eBL cases reacted to fewer antigens than controls, both in Ghana and Uganda (Derkach et al. [1]). IgG reactivity to eleven of the *Pf*EMP1-derived antigens was lower in eBL cases compared to controls in Ghana. A corresponding trend was observed also in the Ugandan study group with low IgG reactivity to three *Pf*EMP1-derived antigens. Inverse associations of eBL and IgG reactivity to all CIDR domains were observed, indicating that reduced IgG reactivity in eBL is not associated with the function of *Pf*EMP1.

In young children, when maternal antibodies decrease in circulation, EBV infection occurs and is mostly asymptomatic. The increased risk of eBL is not due to EBV infection alone, but also to recurrent and intense exposure to malaria parasites. The immune system is under relentless stress in children less than 5 years through repeated malarial infections with high parasite burdens. The cumulative exposure over years provides some degree of immunity, but the interaction of *P. falciparum* and B cells is apparently key in the eBL oncogenesis. Proposed mechanisms include extensive expansion of a monoclonal EBV-infected B cell population, suppression of EBV-specific T-cell immunity, reactivation and massive propagation of EBV, and AID-dependent genomic translocation [2].

During the course of malaria, expansion of EBV-infected B cells occurs. The *Pf*EMP1 expressing erythrocytes bind to host endothelial receptors and evade destruction in the spleen, thus expanding *Pf*EMP1 encoding var. genes and, subsequently, various *Pf*EMP1 adhesion phenotypes. *P. falciparum*-infected erythrocytes directly adhere to and activate B cells through *Pf*EMP1 domains [3]. This interaction increases expression of Toll like receptors, in particular TLR7 and TLR 10, subjecting B cells to TLR 9 signalling and persistently activating B cells [3]. *P. falciparum* infection was previously found associated with increased proliferation and transformation of EBV-infected cells both in children with clinical and with asymptomatic malaria [4].

Derkach and colleagues show strong reactivity against *Pf*EMP1 antigens in the control individuals (Derkach et al. [1]). This suggests that children were obviously exposed to malaria and the absence of clinical symptoms is a result of naturally acquired immunity, the ability to restrain the parasite burden.

A yet other mechanism is suppression of EBV-specific T-cell immunity. In malaria, EBV-specific T cells fail to control EBV-infected cells, causing abnormal proliferation of EBV infected B cells as observed in eBL [5].

EBV viral loads are also associated with the development of eBL [6]. Reactivation of EBV may also be induced by *P. falciparum*. It was shown that EBV-DNA levels in plasma of children and pregnant women with malaria were higher than among those without malaria, indicating that viral replication is increased during malarial episodes [7]. Binding of latently EBV-infected B cells to *Pf*EMP1 directly switches the virus into a lytic replication cycle and CIDRα1 stimulates EBV production [8].

P. falciparum malaria may also promote genomic instability and activation-induced cytidine deaminase (AID)-dependent B cell lymphoma [9]. The intensity of malaria transmission is associated with AID expression levels in the presence of EBV. Therefore, AID is a key player that induces *Plasmodium*-induced lymphomagenesis [10].

Taken together, malaria is not a direct trigger of eBL, but infection rather modifies the lymphoma phenotype and the onset of eBL. Understanding such multifactorial mechanisms involved in the development of eBL has important repercussions in piecing together eBL carcinogenesis.

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E-mail address: velavan@medizin.uni-tuebingen.de.

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Disclosure

The author declared no conflicts of interest.

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