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REVIEW ARTICLE

Endemic Burkitt lymphoma – an aggressive childhood cancer linked to *Plasmodium falciparum* exposure, but not to exposure to other malaria parasites*

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Burkitt lymphoma (BL) is an aggressive non-Hodgkin lymphoma. The prevalence of BL is ten-fold higher in areas with stable transmission of *Plasmodium falciparum* malaria, where it is the most common childhood cancer, and is referred to as endemic BL (eBL). In addition to its association with exposure to *P. falciparum* infection, eBL is strongly associated with Epstein–Barr virus (EBV) infection (>90%). This is in contrast to BL as it occurs outside *P. falciparum*-endemic areas (sporadic BL), where only a minority of the tumours are EBV-positive. Although the striking geographical overlap in the distribution of eBL and *P. falciparum* was noted shortly after the first detailed description of eBL in 1958, the molecular details of the interaction between malaria and eBL remain unresolved. It is furthermore unexplained why exposure to *P. falciparum* appears to be essentially a prerequisite to the development of eBL, whereas other types of malaria parasites that infect humans have no impact. In this brief review, we summarize how malaria exposure may precipitate the malignant transformation of a B-cell clone that leads to eBL, and propose an explanation for why *P. falciparum* uniquely has this capacity.

Key words: Endemic Burkitt lymphoma; immunology; malaria; molecular microbiology; pathology of tumours; Plasmodium falciparum; PfEMP1.

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Endemic Burkitt lymphoma (eBL) is the most common childhood cancer in tropical Africa, where almost half non-Hodgkin lymphomas in children are eBL (1). Disease progression is rapid, owing to the very high rate of cell division in eBL, and in the absence of treatment, eBL is invariably fatal. Although high cure rates are achievable with intensive chemotherapy (2, 3), eBL is a disease of the financially underprivileged (4), and prognosis is therefore very poor at many sites where the disease occurs, due to late presentation, lack of access to efficient and sustained treatment, and premature withdrawal from therapy (3, 5). Health service priority setting is obviously particularly difficult in low-income countries, but treatment of curable disease is a fundamental right and encouraging results can be obtained with limited investment (3, 6). Concurrently, basic research must continue, to improve the understanding of molecular pathogenesis of eBL and of the immune responses aimed at controlling it.

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EARLY FINDINGS AND SPECULATIONS

The disease that is now known as eBL was first described in detail in 1958 (7), although scattered earlier reports exist. It was reported as a common tumour in African children, mostly located in the face (maxilla or mandible) or in the abdomen. It was soon realized that the tumour is a non-Hodgkin type lymphoma (8), with a striking geographical restriction of eBL to tropical Africa (9). This led to speculations that eBL pathogenesis involved a vector-borne virus (10). The search for such a virus in eBL cell cultures soon yielded the virus now known as Epstein–Barr virus (EBV) (11). Epidemiological evidence supported a causal relationship between early-age EBV infection and eBL (12), and almost all eBL tumours are EBV-positive (13), but EBV is not transmitted by insects and is not by any means restricted to tropical Africa. Furthermore, EBV does not normally lead to malignant transformation of the infected cells, although the virus has oncogenic potential. Thus, EBV appears to be a necessary, but not sufficient requirement for the development of eBL. Detailed reviews of the role of EBV in eBL pathogenesis can be found elsewhere (14).

The peculiar geographical restriction of the incidence of the cancer quickly led to speculations regarding a possible involvement of malaria parasites in its pathogenesis (15, 16), and this hypothesis was soon widely adopted, based on a range of indirect lines of evidence (17). Prominent among them, and implicating *P. falciparum* specifically rather than malaria parasites in general, was the contemporary report of a similar cancer in Papua New Guinea (18), where transmission of this parasite was similar in intensity to what is found in Africa. Furthermore, it appeared to be almost absent from tropical Central America (19), where *P. falciparum* transmission does occur, albeit at much lower intensity than in Africa. More recent data indicate that eBL is also essentially absent in India, where most malaria infections are caused by *P. vivax* rather than by *P. falciparum* (20). Finally, the incidence of eBL seems to be declining in parallel with the decline in *P. falciparum* incidence in Africa in recent years (21).

THE RELATIONSHIP BETWEEN EBL AND *P. FALCIPARUM* INFECTION

The epidemiological relationship between eBL and *P. falciparum* malaria has been confirmed repeatedly since it was first observed. Although the molecular details remain unresolved, *P. falciparum* infection appears to affect eBL aetiology both indirectly and directly (22, 23). Proliferation of latently EBV-infected B cells is mainly controlled by cytotoxic T cells and by NK cells (24, 25), but *P. falciparum* malaria appears to compromise these immune responses, allowing increased virus replication (26–29). While these *in vitro* studies may not accurately reflect the *in vivo* immune status of the donors, they are supported by studies showing increased EBV loads in *P. falciparum* malaria (30) and in children regularly exposed to this parasite (31, 32). It does indeed seem plausible that *P. falciparum* exposure indirectly increases the risk of EBV-induced malignant B-cell transformation by compromising cell-mediated control of EBV replication, as the viral protein EBNA3 promotes genomic instability and the genetic translocations that lead to eBL (33, 34).

In addition to the above indirect role of *P. falciparum* in eBL pathogenesis via a negative impact on immune control of EBV-infected B cells, the parasites may also play a more direct role. *P. falciparum* infection leads to marked B-cell activation, and individuals living in *P. falciparum*-endemic areas have substantially higher levels and synthesis rates of immunoglobulins compared with non-endemic controls (35, 36). B-cell activation and differentiation depend critically on activation-induced cytidine deaminase (AID), which is the key enzyme required for the class switching and somatic hypermutation that are central processes in B-cell maturation in germinal centres (37). The function of AID involves double-strand DNA breaks, and can therefore occasionally lead to off-target translocations. This risk increases with the level of AID, and *P. falciparum* exposure has been associated with increased AID expression (38, 39). The combination of increased frequencies of EBV-infected B cells and the relentless malaria-related induction of B-cell activation with associated increases in levels of AID may well be what precipitates the disastrous chromosomal translocation of the oncogene *c-myc* into one of the antibody gene loci (40, 41). That translocation is the hallmark of eBL and causes unrestricted proliferation of the affected B-cell clone (42). What is much less clear is why this exclusively happens in *P. falciparum* infection, but not in other diseases that cause massive B-cell activation, including infections with other malaria parasite species.

A PUTATIVE ROLE OF PFEMP1 IN EBL PATHOGENESIS

It would seem plausible that the answer to this question is related to features that sets

P. falciparum apart from the other species of *Plasmodium* that can infect humans. One such feature is the high efficiency with which mature *P. falciparum*-infected erythrocytes (IEs) adhere to the vascular lining in many tissues. This ability is an important virulence factor, as it allows the parasite to escape destruction of IEs in the spleen (43). It not only facilitates the development of much higher parasitaemias than seen in other human malaria infections, but also leads to vascular obstruction and tissue inflammation, which can be fatal if occurring in key organs such as the brain (44). The most important ligand mediating IE sequestration is the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) (45). Various members of this protein family have affinity for different host endothelial receptors, such as endothelial protein C receptor (46) and intercellular cell adhesion molecule 1 (47), and some variants are even capable of adhering to several at the same time (48, 49). Importantly, other human-pathogenic species of malaria parasites do not possess PfEMP1-like proteins (50).

PfEMP1-specific antibodies start to develop early in life, and they constitute an important component of the acquired immune response to *P. falciparum* malaria (45). A possible role for PfEMP1 in eBL pathogenesis appeared, when it was discovered that a subset of a particular PfEMP1-specific structural element, could bind with low affinity to B-cell receptors (BCRs) and act as polyclonal B-cell activators that induce the lytic cycle in B cells latently infected with EBV (51–53). The cysteine-rich inter-domain region α (CIDRα) domains of PfEMP1 appeared mainly to activate memory B cells and to protect them from apoptosis (54). If this was indeed an important element of eBL pathogenesis, any EBV-positive B-cell expressing a BCR with affinity for CIDRα might be vulnerable. Therefore, PfEMP1-specific B cells would be expected to be particularly prone (unless the interaction between CIDRα and BCR is completely independent of the BCR antigen specificity). This would provide an explanation for the unique role of *P. falciparum* in eBL pathogenesis, but at present, there is admittedly not much evidence in favour of it. Some early studies found evidence of antibody secretion by eBL tumour cells (55), whereas others did not (7). Furthermore, no convincing evidence of differences in malaria-specific antibody reactivity between eBL patients and sympatric controls was found (55, 56). More recently, negative, positive and absent associations for various non-PfEMP1 antigens have been reported (57, 58), whereas a very recent, PfEMP1-centric, study found lower reactivities to several PfEMP1 constructs, including CIDRα (59).

DIFFICULTY DEMONSTRATING RELEVANCE DOES NOT NECESSARILY IMPLY LACK OF RELEVANCE

This lack of direct evidence is not encouraging for a PfEMP1-centric explanation, but does not necessarily rule out a role for PfEMP1 in the aetiology of eBL. In areas, where *P. falciparum* transmission is stable and intense – that is, the areas where eBL is most prevalent – malaria is a disease of young children, as substantial clinical protection is acquired over a period of several years (60). As a result, severe disease after five years of age is the exception, which is several years earlier than the peak incidence of eBL (22, 61). However, available evidence suggests that extended periods of low-density parasitemia continue to occur throughout life, kept at sub-clinical and often even sub-microscopic levels by acquired immunity. Furthermore, it appears that the transition from clinical and severe disease early in life to low-density and inconspicuous parasitaemia later on reflects an ordered and sequential acquisition of IgG to different types of PfEMP1 (62–64). Antibodies to PfEMP1 variants associated with severe disease are acquired first, because they tend to be fairly conserved among different parasite clones. Furthermore, they allow high effective multiplication rates of the parasites, and thus tend to dominate in patients with little or no protective immunity (65–68). Substantial immunity to the variants associated with uncomplicated and sub-clinical infections is acquired only after the initial selective advantage of virulent PfEMP1 has been attenuated by specific IgG (69, 70). Sterile immunity to those 'avirulent' PfEMP1 variants is probably never achieved, because they are antigenically very diverse and allow only low effective multiplication rates. Conceivably, they are thus perceived by the immune system as being less 'dangerous', and hence less immunogenic (71). Nevertheless, they are very useful to the parasites, as they allow untreated infections to persist for years (72, 73). Although this premunition type naturally acquired immunity protects substantially from severe malaria and clinical disease, it also has negative impacts on the health of those infected (74), and we speculate that risk of eBL may be among them. Indeed, it may be the chronic strain on the immune system imposed by persistent parasitaemia, rather than the acute immune response to overt clinical episodes, that links the two diseases. That could explain the temporal difference in the peak incidence of severe *P. falciparum* malaria and eBL. However, it would also make the search for the identity of the putative PfEMP1 variant(s) inherently difficult, because the candidate(s) would be

expected to be variant(s) showing high inter-clonal diversity. It may be noteworthy in this context that a recent study of adult BL patients in the United Kingdom noted indirect evidence of exposure to *P. falciparum* 2–10 years prior to the cancer diagnosis as a significant eBL risk factor (75). The study did not provide any details regarding the geographical origin of the patients studied, but most appeared settled U.K. citizens. We agree with the authors that their findings warrant further studies.

EBL, MALARIA, AND SICKLE CELL ANAEMIA

Sickle cell disease is a serious haemoglobinopathy caused by homozygous carriage (HbSS) of a recessive mutation in the β-globin subunit of haemoglobin. Despite the serious morbidity of sickle cell disease, the HbS gene is maintained at high frequencies (only) in areas with stable *P. falciparum* transmission (76). This is because heterozygous carriers (HbAS) are not only healthy, but also markedly resistant to severe *P. falciparum* malaria compared to sympatric individuals without the mutation (HbAA) (77). Considering the link between eBL and *P. falciparum* malaria outlined above, one might expect that sickle cell trait (HbAS) individuals would therefore also be protected from eBL. While some early studies did support the idea of such a relationship, their statistical power was low (78, 79). Furthermore, other studies, and in particular a recent and much better powered study, found no evidence that HbAS individuals are any less likely to develop eBL than HbAA individuals (80, 81).

HbAS-dependent protection against malaria is mainly against severe disease and appears to involve an accelerated acquisition of protective immunity (82, 83). Remarkably, it has little impact on susceptibility to infection *per* se and asymptomatic infections (84), and may even lead to increased antigenic diversity of chronic infections (83). If persistent low-density parasitaemia (probably maintained by parasites expressing highly diverse, low-virulence PfEMP1 variants) is what links *P. falciparum* to eBL, then it is not surprising that HbAS confers little protection against eBL.

CONCLUDING REMARKS

Endemic Burkitt lymphoma is a devastating cancer of African children. High cure rates are achievable, but are often not realized due to financial and logistic constraints. Research aimed at elucidating the molecular details of the disease pathogenesis and immune responses may help overcome some of these obstacles. Novel scientific insights regarding the interplay of cancers and infections are needed to improved therapeutic interventions against them. This research should be multi-disciplinary, and involve clinicians, oncologists, epidemiologists, immunologists, pathologists, and parasitologists in a concerted effort.

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