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The double-edged sword of *Plasmodium falciparum*: malaria and a predisposition to B-cell malignancy?

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Retrospective analyses of cord blood and neonatal blood spots have identified driver mutations, including fusion genes associated with B-cell precursor acute lymphoblastic leukaemia (BCP-ALL), demonstrating that the initiating genetic events often occur in utero. During foetal development, DNA double-strand breaks arise during normal lymphoid development, including V(D)J recombination, and may also occur under the proliferative stresses of foetal haematopoiesis and responses to intrauterine stress. Erroneous repair of these breaks can generate alterations in genes regulating B-cell development, resulting in developmental arrest and the formation of pre-leukaemic clones. Because such alterations are detected in small neonatal blood samples, lineage-restricted clones have undergone substantial expansion by birth. Yet only a very small proportion of individuals in whom such precursor cells are detected subsequently develop clinically apparent BCP-ALL. Additional genetic and environmental "hits" are therefore required for malignant transformation. Epidemiological studies and murine models implicate childhood infections and alterations in the gut microbiome as potential contributors to disease progression. No single infectious agent has been identified as causative to date. Instead, experimental evidence suggests that leukaemogenesis may reflect an aberrant immune response to naturally occurring infections. Indeed, both epidemiological and experimental data indicate that exposure to common infections early in life may eliminate pre-leukaemic clones and thereby reduce the risk of BCP-ALL. (1)

In the current issue of this journal, Rugwizangoga and colleagues report findings that suggest a possible link between *Plasmodium falciparum* exposure and the development of ALL in East Africa. (2) They observed significantly higher titres of anti-Histidine Rich Protein-2 (HRP-2) IgG3 and lower titres of anti-SE36 IgG1 in pretreatment blood samples from 156 patients with ALL compared with 101 patients with acute myeloid leukaemia (AML) and 94 blood donors. HRP-2 is a soluble protein secreted by *P. falciparum*, whereas SE36 is a recombinant fragment derived from the N-terminal domain of serine repeat antigen-5. Both antigens derive from protein expressed during blood-stage infection. IgG3 has a relatively short half-life of approximately seven days, compared with around 21 days for IgG1 and IgG2. Consequently, for the purposes of this study, anti-HRP-2 IgG3 serves as a marker of recent *P. falciparum* exposure, while anti-SE36 IgG1 reflects prior exposure to the

parasite. Although preliminary, these observations are intriguing and warrant further investigation.

The findings are particularly relevant in the context of childhood cancer epidemiology in East and sub-Saharan Africa. Whereas ALL is the most common childhood malignancy in most parts of the world, endemic Burkitt lymphoma (eBL), another B-cell malignancy, is considerably more prevalent in this region. More than 90% of children in East Africa acquire Epstein-Barr virus (EBV) infection within the first year of life, whereas many children in Europe and North America remain EBV-seronegative until adolescence. EBV infection persists lifelong and promotes B-cell proliferation and survival. *P. falciparum* infection is also acquired early in life, typically before five years of age, and remains a major cause of childhood mortality. (3) Chronic malaria exposure induces sustained polyclonal B-cell activation and aberrant activation of activation-induced cytidine deaminase (AID). Dysregulated AID activity causes off-target DNA damage and contributes to the characteristic *MYC* translocation that underlies eBL. Consequently, eBL is widely regarded as a disease driven by the interaction of two pathogens. Although severe *P. falciparum* infection causes substantial childhood mortality, chronic exposure among survivors may increase the pool of EBV-infected B cells and promote AID activity, contributing to the development of eBL. (4)

Whether similar mechanisms contribute to ALL remains uncertain, but the findings reported by Rugwizangoga and colleagues raise this possibility. Although differences in cancer registration and diagnostic access complicate direct comparisons, reported incidence rates of childhood ALL are generally lower in East Africa than in South Asia. (5) Unlike East Africa, Burkitt lymphoma is generally sporadic rather than endemic in South Asia, and malaria is more often caused by *Plasmodium vivax*, except in limited areas of intense *P. falciparum* transmission. An intriguing but untested hypothesis proposes that neonatal EBV infection may attenuate inflammatory responses to repeated *P. falciparum* infections, thereby enhancing survival from malaria while increasing the later risk of eBL. (6) The critical oncogenic events that drive eBL occur postnatally, whereas the initiating lesions in BCP-ALL arise in utero. This distinction raises an interesting question: could early-life exposure to *P. falciparum* alter the fate of pre-leukaemic clones, thereby contributing

to the lower incidence of BCP-ALL observed in East Africa? Notably, the median age at diagnosis in the current study was 11 years, considerably older than the typical age of 4 to 5 years reported in South Asia, though we do not know if the age-related genetic subtypes of childhood ALL are retained. Within the framework of EBV-malaria cooperation, AID activity is central to the pathogenesis of eBL. In contrast, murine studies suggest that AID is not required for the development of BCP-ALL, at least in a *PAX5* haploinsufficient background. (7) This raises several other questions. Are there *P. falciparum* proteins capable of directly promoting B-cell leukaemogenesis? Does malaria interact with EBV in the pathogenesis of ALL, as it does in eBL? In this setting, *P. falciparum* may represent a double-edged sword (Figure 1). Factors that promote survival after infection in early childhood could simultaneously increase the long-term risk of B-cell malignancy. As malaria vaccination programmes are expanded across Africa, it will be important to determine whether this will influence the incidence, age distribution, or biological characteristics of childhood BCP-ALL? Addressing these questions will require prospective studies conducted in populations where both malaria and early-life EBV infection are endemic, and where the biological consequences of their interaction can be directly examined.

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Legend for Figure 1

Hypothetical model linking *Plasmodium falciparum* exposure to the fate of prenatal pre-leukaemic B-cell precursor clones.

Genetic lesions arising in utero generate clinically silent B-cell precursor pre-leukaemic clones. Following birth, malaria exposure may have contrasting effects: immune activation associated with early infection may promote clone eradication, whereas chronic or recurrent infection, particularly in the setting of early EBV acquisition, may favour clone persistence and progression toward acute lymphoblastic leukaemia. This model is hypothetical and remains to be tested experimentally and epidemiologically.

Figure 1

