Austin Journal of Clinical Immunology

Austin Publishing Group

Open Access Full Text Article

Mini Review

Translating Burkitt's Lymphoma Research into Viable Solutions for Developing Countries

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Received: August 25 2014; **Accepted:** September 15 2014; **Published:** September 20 2014

Abstract

50 to 70% of all newly diagnosed childhood cancers in Sub-Saharan Africa are due to Endemic Burkitt's lymphoma (eBL). It occurs mainly in malaria holoendemic areas where the climate supports *Plasmodium falciparum* mosquitoes and causes year-round malarial infection. eBL risk is highest in children with high antibody titers to both Epstein - Barr virus (EBV) and malaria. The peak eBL incidence in children coincides with peak malarial antibody genetic diversity, which occurs around 5 to 9 years of age. The precise mechanisms by which malaria influences the disease, however, are not well understood. eBL disproportionately affects particular tribal groups within malaria holoendemic areas, which suggests a genetic component to the disease. Congruently, there are polymorphisms within the CD36 receptor that cluster in particular tribal groups in similar geographical areas and that could provide candidate genetic markers for eBL screening and prevention. CD36 is a cellular surface receptor found on platelets, red blood cells, macrophages, vascular endothelial cells and other cell types. It plays an important role in maintaining general homeostasis or internal cellular balance in organisms. This article reviews what is known about eBL pathogenesis and discusses how research into the role of malarial antibody diversity and CD36 deficiency in eBL risk could lead to viable solutions for eBL prevention in the resource-limited settings that are worst-affected by the disease.

Keywords: Burkitt's Lymphoma; Malaria; CD36; *Plasmodium falciparum*; Single Nucleotide Polymorphisms; Resource Limited Settings

Abbreviations

B Cell: Bone Marrow-Derived Immune Cell; CD8: Cluster of Differentiation 8; CD36: Cluster of Differentiation 36; eBL: Endemic Burkitt's Lymphoma; EBV: Epstein-Barr Virus; GC: Germinal Center; HIV: Human Immunodeficiency Virus; HLA-DR7: Human Leukocyte Antigen – DR7 ; Ig: Immunoglobulin; IL-10: Interleukin 10; LDL: Low Density Lipoprotein; MHC: Major Histocompatibility Complex; SE36: *Plasmodium falciparum* serine repeat antigen 5; SNPs: Single Nucleotide Polymorphisms; T-cell: Thymus-derived Immune Cell; WHO: World Health Organization

Background

Epidemiology

Denis Burkitt described Burkitt's lymphoma in 1958 while he was working at Mulago Hospital, Kampala, Uganda, East Africa, a region where the incidence of BL continues to be far higher than any other part of the world [1,2]. In 1969, the World Health Organization (WHO) devised a histopathological diagnostic scoring system for the tumor [3]. It has since been found throughout the world and is now classified into African or endemic BL (eBL), sporadic BL and immunodeficiency-related BL [4]. Incidence is estimated at one case per 100,000 children in low incidence areas to about 10 per 100,000 children up to 14 years of age in Africa. The incidence in the USA and Europe is much lower at 0.13 per 100,000 in children of the same age range [5]. Most cases in Africa occur within a geographical band that extends 15º on either side of the equator referred to as the "Lymphoma Belt" [6].

EBV and Burkitt's lymphoma

EBV is a very common herpes virus that is found as a latent infection in the memory (Bone Marrow derived) B cells of over 95% of the human population [5,7]. It has been associated with several types of cancer. Virtually all eBL tumor cells are EBV+ and express EBV latent genes. Antibodies to EBV are raised months or years prior to the development of eBL and have been shown to correlate with disease burden. BL tumor genesis is the result of a mutation and relocation of the c-myc proto-oncogene which uncouples it from upstream genetic regulatory elements. The resulting B cell lymphoma is a very rapidly dividing yet apoptotic cell mass. In order for abnormal cells to survive and multiply, EBV-containing B cell precursors must reach the memory cell compartment of the thymus during their development. They must interact with cells in the germinal center (GC) before maturing into memory cells. Normally, during these interactions, B cells that are defective and produce low affinity antibodies are not permitted to leave the germinal center but are induced to undergo apoptosis. EBV infection disrupts this selection process and allows for the survival of memory B cells that are tumorigenic.

Malaria and Burkitt's lymphoma

Protective humoral immunity to malaria is only acquired following a decade or more of exposure to the parasite. The parasite has a vast array of immunogenic antigens, and it is not known which antibodies are important for protection. The best evidence for a role of malaria in the pathogenesis of eBL is the correlation between eBL incidence in children and regions of holoendemic malaria where malaria transmission takes place throughout the year [3,8-10]. There

Citation: Kibirige CN. Translating Burkitt's Lymphoma Research into Viable Solutions for Developing Countries. Austin J Clin Immunol. 2014;1(4): 1018.

is an absence of BL in arid regions within the "lymphoma belt" where malaria is at low levels [11]. eBL develops at a later age in individuals who have migrated from malaria-free high altitude areas to lower, malaria-endemic areas [11]. BL incidence has been reduced in areas where interventions such as drug treatment and bed nets have controlled the intensity of malaria infection and transmission although these effects have not always been lasting [7,11].

The types of anti-malarial antibodies present in a child while he/she is at risk for eBL reflect a) the malarial antigens to which the child has been exposed and b) the frequency of these exposures. Recurrent malaria infections in holoendemic areas cause partial immunity to malaria which leads to sustained high-density parasitemia and an intense disruption of memory B-cell development [3,8]. *Plasmodium falciparum* is the most likely candidate for BL induction because it disrupts the immune response to EBV [7,12] and induces B cell hyperplasia or over-growth [9].

There is evidence that an individual's specific *P. falciparum* antibody repertoire is associated with eBL risk. For example, antibodies against the malarial SE36 antigen have been shown to correlate with a reduced risk for eBL while antibodies against HRP-III have been associated with greater eBL risk [13]. Furthermore, it has been found that the genetic diversity of *P. falciparum* strains within individuals peaks between 5 to 9 years of age in holoendemic areas of East Africa [14]. This time frame coincides with a peak in eBL incidence [14,15].

Despite the many opportunities for malaria to influence EBV infection levels, the timing of primary EBV infection, peak malarial morbidity and mortality, and peak eBL incidence do not coincide. Specifically, peak malarial morbidity and mortality precedes peak eBL incidence and primary EBV infection precedes both of these. This suggests that malarial infection continues to exert a considerable amount of pressure on the immune response even after the peak in its morbidity and mortality. The prolonged interaction among these co-infections sets up the immunological environment necessary for tumorigenesis.

Host genetics and Burkitt's lymphoma

As already mentioned, endemic Burkitt's lymphoma disproportionately affects certain tribal groups in malaria holoendemic areas which suggests a genetic component to the disease. A few genetic associations have already been made with Burkitt's lymphoma to date. The HLA-DR7 MHC haplotype, for example, has been associated with an increased risk of developing BL in a number of studies [16], as has a polymorphism in the gene encoding IL-10 [17]. These associations are not linked to any particular tribal group and it is therefore highly likely that there are additional polymorphisms that predispose particular people to the development of BL.

A good candidate gene for malaria-linked biomarkers that could be associated with eBL risk is CD36. C36 is a receptor that is expressed on the surface of a variety of cells including vascular endothelial cells, macrophages and platelets. CD36 binds oxidized LDL, thrombospondin and anionic phospholipids and plays an important role in organismal homeostasis. CD36 deficiency, which involves the down regulation of CD36 on micro-vascular endothelial cells, has been implicated in aberrant angiogenesis and subsequent tumor formation in various pathogenic mechanisms [18]. The down-regulation of CD36 on macrophages may affect their ability to clear abnormal and apoptotic cells and provide an additional mechanism for the enhanced risk of tumorigenesis [12]. CD36 deficiency has been linked to the disease severity of Kaposi's sarcoma-associated Herpes Virus for example, which disproportionately clusters with severe malaria epidemiologically [19].Various studies have shown that there are particular CD36 SNPs that are over-represented in certain African populations in malaria endemic areas [20]. This suggests that evolutionary selection by malaria has shaped genetic variation at the CD36 gene locus. Some of these SNPs have been shown to result in deficiencies in the function of the CD36 receptor that could explain some of the malarial phenotypes that result. To date, no study has looked specifically at the association between SNPs in the CD36 gene and eBL risk.

Studies suggest that antigens expressed on the surface of infected erythrocytes bind directly to CD36 on endothelial cells, causing the sequestration of infected erythrocytes in peripheral tissues and preventing their clearance during the blood's passage through the spleen [21]. This results in severe malarial symptoms.CD36 deficiency affects non-opsonizing (antibody independent) phagocytosis which is an important innate mechanism for controlling parasite numbers [22]. This suggests that a down regulation of CD36 could be evolutionarily advantageous to individuals living in malaria holoendemic areas by preventing severe malarial symptoms. This could explain why CD36 polymorphisms are prevalent in equatorial Africa. Animal studies strongly corroborate this theory and show lower parasitemia and enhanced survival in CD36-deficient mice compared to normal control mice of similar genetic background [22].

Human epidemiological studies looking at CD36 SNPs and risk of malaria, on the other hand, have yielded very conflicting and confusing results and do not corroborate this theory very well [20,21,23-25]. An explanation for this could be that CD36 deficiency results in increased malarial parasitemia and disease severity in non-holoendemic areas by severely impairing innate (opsonization independent) viral clearance in individuals who are not frequently exposed and are very immune-naïve to malarial infection. CD36 deficiency could paradoxically have a less detrimental and even beneficial effect on individuals in holoendemic areas who have developed a large repertoire of circulating anti-malarial antibodies from a young age. These individuals could have well developed opsonizing phagocytotic mechanisms which compensate for any impairment in innate immunity to malaria [22]. CD36 deficiency could therefore confer a selective advantage in malaria holoendemic areas but have the unfortunate consequence of predisposing carriers of the trait to various cancers including eBL.

Conclusion

Viable solutions for resource-limited settings

Thanks to the effective collaborative efforts that Dennis Burkitt instigated while working in Africa, Burkitt's lymphoma research has played an important role in modern medicine and biomedical research [3]. EBV was discovered by Epstein, Barr and Achong in 1964 while studying a BL-derived cell line [26]. Denis Burkitt showed that BL was extremely responsive to chemotherapy in 1965 which eventually led to a Lasker Award for John Ziegler and Alfred

Ngu in 1972 for the development of a successful BL chemotherapy regimen in the United States [3,27-29]. Y. Manolov and G. Manalova demonstrated chromosomal translocation as a general mechanism for tumorigenesis through their work on eBL tumorigenesis [30]. The Nobel Laureate Harold Zur Hausen elucidated DNA hybridization mechanisms while studying BL tumor cells [31]. Today 90-100% of BL cases in developed countries are successfully cured from the disease.

Despite the significant contributions Burkitt's lymphoma research has made to modern medicine, eBL remains fatal in developing countries. Its incidence remains very high in the regions of Africa where it was initially discovered and characterized. Early stage tumors can be cured with just three cycles of treatment, whereas late stage tumors require 6 or more cycles, and many usually do not respond to treatment. The best predictor of survival is thus early stage of BL at diagnosis. In developed countries, BL is treated in specialized pediatric oncology units that are equipped and staffed to deliver the high-intensity, high-dose, multidrug chemotherapeutic regimens and the intensive supportive care required to effectively treat BL. Such facilities do not exist in and are beyond the reach of most of the countries where the disease is endemic. In rare instances when children are diagnosed in developing countries, the diagnosis is made when the tumor has spread and is no longer easy to treat.

It is imperative that current and future research efforts focus on viable solutions for these resource-limited settings. Protein micro-array technology could help identify a serum-based malarial biomarker of BL, for example, and could lead to the development of cost-effective tools for rapid identification of children at increased risk for BL. Such biomarkers could possibly have application for the follow-up of cases to detect early recurrent or presence of internal minimal residual disease. Such tools could offer a practical way to integrate BL surveillance into established malaria and/or Human Immunodeficiency Virus (HIV) health care activities. It is also important that we consider how genetic screening tools could successfully be applied in resource-limited settings.

Acknowledgement

I would like to thank Dr. Samuel Mbulaiteye, National Cancer Institute, United States and Dr. Alan Scott, Johns Hopkins University, United States, for helpful discussions and ideas that have greatly shaped the opinions in this article. I would like to thank Dr. Joseph B. Margolick for editorial help with this manuscript.

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Austin J Clin Immunol - Volume 1 Issue 4 - 2014
ISSN : 2381-9138 | www.austinpublishinggroup.com

Citation: Kibirige CN. Translating Burkitt's Lymphoma Research into Viable Solutions for Developing Countries. Austin J Clin Immunol. 2014;1(4): 1018.