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Review Article

Epstein-Barr Virus And Burkitt's Lymphoma Pathogenesis: An Unresolved Issue

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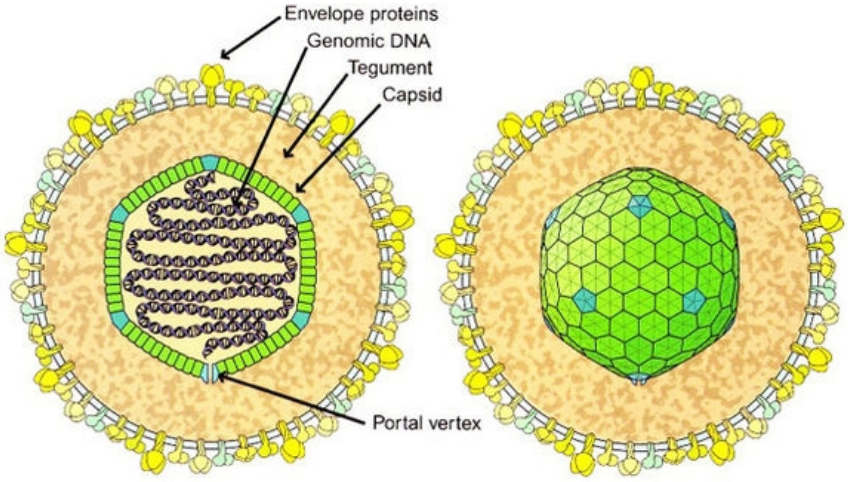
ABSTRACT

Epstein Barr virus (EBV) is a virus known to cause not less than five human malignancies. Its contribution and relationship towards these carcinomas are still not known. Our research showed that a viral protein found in all malignancies associated with Epstein Barr virus. This protein is Epstein Bar nuclear antigen 1 (EBNA-1) and its needed for survival of one of these cancers; EBV-positive Burkitt Lymphoma. When EBNA-1 is inhibited, these tumor cells survival is decreased by inducing apoptosis. In the absence of EBV genome, apoptosis induced by the expression of p53 can be inhibited by expression of EBNA-1. Our study show that this antigen EBNA-1 is critical for EBV-associated Lymphoma survival continuation. Same with other B cell tumors associated with EBV. In understanding any possible therapy against EBV-associated malignancies, efficient inhibitors of EBNA-1 are useful. The main factors believed to play vital roles in the pathogenesis of BL are Genetic instability imposed by activation induced deaminase (AID), Antigenic and/or Polyclonal stimulation of B cell receptor, viral gene products of EBNA-1 and many small non-coding non-polyadenylated RNAs. The role of this virus is difficult to describe despite its related intensives researches. Although positive expectations are raised because of the discovery of two viral microRNA clusters expressed in EBV associated tumors, including Burkitt Lymphoma. This mystery may be solved soon. The main objective of this review is to understand the interplay between viral and cellular factors associated with BL and emphasis is laid on mouse models and cell culture experiment that direct towards these points..

INTRODUCTION:

Initially Burkitt's Lymphoma (BL) was described as a clinical entity seen in Central African children in 1958, by Denis Burkitt. This tumor has some epidemiological features which raised the search for its causative virus leading to the discovery of Epstein Barr virus (EBV) by Epstein et al in 1964. In 1970s and 1980s, it became obvious that this tumor is not restricted to Central Africa alone rather there is less incidence in other parts of the world in its sporadic form[1-3]. It is mostly frequent in HIV positive individuals. Not all BL cases are as of result of EBV infection. About 95% of its occurrence in Central Africa, 40 to 50% of the cases in HIV positive individuals and 10 to 20% of the sporadic cases harbor the viral information and express at least one viral antigen (EBNA1) and several non-coding viral RNAs[4]. There are differences in all BL cases regardless of its epidemiological region by exhibiting one of the three c-myc/Ig chromosomal translocations which results in activation of c-myc gene as a critical moment in development of this disease. The role of EBV in the development of BL has been clearly pointed out in the African cases, but still the pathogenesis remains elusive. BL is high aggressive and Fast proliferating which may be fatal within few months if not treated immediately[5-8]. C-myc is juxtaposed to one of the Ig loci which characterizes BL by the activation of the c-myc oncogene, through reciprocal chromosomal translocations[9]. Also, many BLs are tagged alongside point mutations in the p53 tumor suppressor gene; other defects in the p14ARF-MDM2- p53pathway, or inactivated p16INK4a genes by homozygous deletion or promoter methylation. In this manner, BL inculcates multiple genetic events which can inhibit cellular apoptosis and promote cellular proliferation[10-13]. In endemic areas of BL, virtually all cases are reported to be in association with EBV. EBV uses multiple viral genes to induce and sustain proliferation of infection B cells. Most of these genes are not expressed in BL tumors making it hard to understand how EBV contributes to the survival of BL tumors. Only one viral protein-Epstein-Barr nuclear antigen 1 (EBNA-1) function is consistently expressed in BL cells are required for their survival[14-17].

Fig:1 Epstein Barr Virus structure



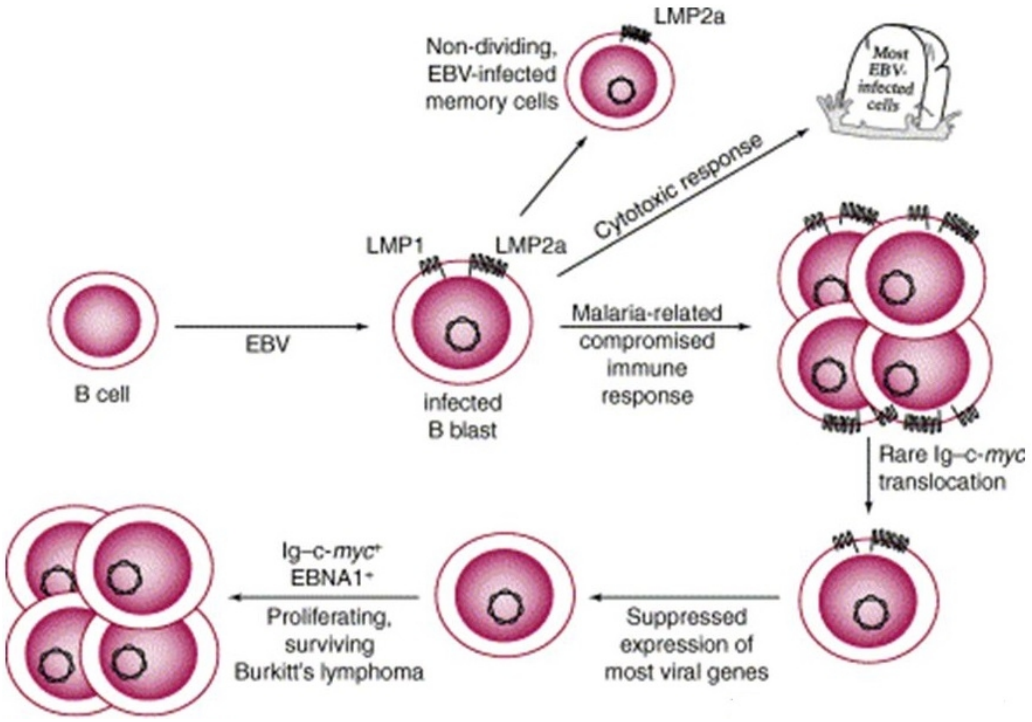
The highest incidence of childhood cancer is BL in the equatorial Africa. Climatic conditions are also related the geographic distributions and coincides with regions where malaria is endemic[18]. These cancers are featured as reciprocal translocation from chromosome 8 near or at the c-myc locus to either one of the light chain loci on chromosome 2 or 22, or the immunoglobulin chain locus on chromosome 14 (80. P.100 of cases)[19-22]. This translocation activates the transcription of the protooncogene c-myc. Development of the tumor can occur maybe by the deregulation of c-myc. The Study of Burkitt's lymphoma led to the discovery of how viral infection and tumor development in humans are associated[23]. All BL cells contains the EB virus implicating it to be a likely etiology factor. Expression of the virus is diminished essentially to small non-coding RNA, non-polyadenylates, and a nuclear protein EBNA1 which is cannot be exempted for maintenance of EBV genome in infected cells. EBNA expression

in transgenes causes lymphoma in mice and could play a role in the expression of the c-myc gene associated in translocations[24-27].

Molecular Biology:-

Epstein-Barr virus is an omnipresent gamma herpes virus which infects about 90% of people studied in most populations and its life-long latency is established in B cells[28-33]. The latency programs of EBV is complicated allowing the virus to manipulate differentiation of B cells and establishing a long-term latency in memory B cell reservoir[34]. Three patterns of this latent infection exists. Features of Latency III include expression of all the EBV latency genes (EBNA1, 2, 3a, 3b, 3c and LP), small noncoding RNAs (EBERs) and latent membrane proteins (LMP1 and LMP2)[35-39]. This model of infection is seen during the primary infection of the B cells and in EBV positive post-transplant lymphoproliferative disorders (PTLDs)[40-41]. EBV latency III is also associated with activation and proliferation of B cells, initially because of the roles of LMP1 and EBNA2 in B cells transformation. EBV switches to latency II expressing LMPs and EBNA1 in germinal center B cells. This second expression may drive the differentiation of B cells into memory B cells[42-45]. Memory B cells exist as the long term latent reservoir of EBV, where downregulation of all latent protein may be expressed. Only the EBERs and EBNA1 are constantly seen in BL cells of EBV+BL, regardless of the clinical subtype. This model is considered that Latent 1 expression of EBV. In minority cases, BLs with LMP2A expression or with EBNA1, 3a, 3b, and 3c expression have been reported. Cell survival and protect of BL cells may also be promoted by EBV infection[46-48].

Fig:1 Burkitt Lymphoma and EPV



Diagnosis of Burkitt Lymphoma

Histologically, the representation of BL is distinctive. At nether magnification, the feature "starry sky" pattern may be seen on hematoxylin and eosin staining[47]. This pattern comprises of a blue background of closely packed, medium-sized round basophilic nuclei which forms the sky on which these stars of tangible-body interspersed macrophages are scattered. At an elevated magnification, the lymphoma cells are seen as intermediate sized, monomorphic lymphocytes with slight blue cytoplasm. The nuclei are circular with multiple small nucleoli and lacy chromatin[48]. On aspirate smears or touch imprints, these cells are remarkable for cytoplasmic lipid vacuoles. Plasmolytic variant is rare, that is frequently seen in children and immunodeficiency-associated subtypes. This variant is remarkable for its high polymorphism with a slightly eccentric nucleus with a single central nucleolus[49-50]. Burkitt-like or Atypical Burkitt lymphoma is the other variant, which is characterized by higher pleomorphism in size and

shape of the lymphoma nuclei containing more prominent nucleoli. Typically, Burkitt's Lymphomas express monotypic surface IgM, bcl-6, CD20 and CD10. They also have an MIBI/Ki-67 proliferation fraction greater than 95%. They typically don't express bcl-2, TdT or CD5. The expressions of bcl-6 and CD10 is preferable to a germinal center (GC) origin for BL, which has been reported in gene expression analysis of BL cells[51]. The origin of germinal center of BL is constantly aligned with the evidence that MYC translocation occurs and an error of somatic hyper-mutation or class switching.

Therapy of Burkitt Lymphoma/Leukemia

Previously unrelenting prognosis of BL patients with 2-year disease free surviving ratio have been greatly improved by new therapeutic regimens approaching 90% in some series[52]. Advancements in improving the therapy include, shorter intensive courses of chemotherapy with higher doses of alkylating agent in combination with intrathecal therapy, together with careful preventive management of tumor lysis syndrome. Also, other two therapy regimens which are not based on the BNHL studies have been used. It has been reported by MD Andersen that hyper-CVAD (high dose cyclophosphamide, doxorubicin, vincristine and dexamethasone alternating alongside methotrexate and cytarabine) led to a 3-year overall survival (OS) of 49% in an older patient population[53]. Analysis of 81 sub-population of patients 60years below showed a 3-year OS of 77%. This result is comparable to the ones in the Magrath and its modified regimens. CALGB regimen (i.e., cytoreduction plus cyclophosphamide and prednisone followed by three cycles of ifosfamide, vincristine, etoposide, cytarabine, methotrexate, and dexamethasone alternating with cyclophosphamide, doxorubicin, vincristine, methotrexate and dexamethasone was reported to have a 4-year disease-free survival of 50%; however, few patients completed all cycles of therapy, due to high toxicities, most especially neurologic toxicity[54]. As previously reported, immunodeficiency-associated BL may be treated with high dose intensive chemotherapy, it also can be treated with concomitant HAART therapy in the case of HIV or by removal of immunosuppression in solid organ transplant patients[55-56].

High dose chemotherapy followed by Autologous bone marrow transplantation (BMT) as consolidation therapy has been used to treat BL with both positive and negative success. A phase II study reported comparable 5-year OS and EFS between patients on standard chemotherapy only and those who were given autologous BMT after a short intensive avoiding high dose methotrexate and cytarabine. Nonetheless, the lack of a clear gain for most patients combined with the supplemental morbidity from BMT has prevented more extensive use of autologous BMT in first line therapy[57]. A Blood and Marrow Transplantation group in Europe backwards review of auto BMT as a salvage therapy for relapsed Burkitt's Lymphoma in second or greater remission showed that a 3-year OS of 72% in patients in first complete remission, 7 % OS in chemo-resistant and 37% in chemo-sensitive relapsed patients. Lesser critical investigations are attributed to allogeneic BMT[58-59]. Retrospective report has shown that patients receiving autologous BMT have had a longer OS than those receiving allogeneic BMT. Even with few other reports, no large prospective trials have shown an in-depth benefit of allogeneic BMT.

New Therapeutic Agents

An anti CD20 monoclonal known as Rituximab, that induces death of B cells has been included in hyper-CVAD-, CHOP- and EPOCH- containing regimes with hopeful preliminary results. Other trials with this and prospective drugs are in progress. There is a high expectation for the synergistic actions of chemotherapy and immunotherapy in BL. Ongoing Molecular-targeted therapies under include histone deacetylase inhibitors, selective serotonin reuptake inhibitors, antisense oligonucleotides to myc, proteasome inhibitors and cyclin-dependent kinase inhibitors, all of which have been used on Burkitt-derived cell lines in vitro. Though, none has made its way into clinical trials[60].

Future perspective

Now Burkitt initially described BL as a common tumor among African children, it became unforeseeable that this specialized tumor would become an important milestone for cancer research. This lymphoma not only covered the space between RNA tumor virus research in animals and cytogenic aberrations as the causes leading to development of leukemia and other lymphomas, but also bridged the gap between DNA and RNA tumor virus research. Ironically, although researchers have made far progress unraveling the actions of cellular protooncogenes like c-myc as well as the biology and molecular biology of EBV, the contribution of EBV molecularly to the pathogenesis of BL is still far from being understood. Another problem is the

lack of an appropriate experimental system in which the pathogenesis of BL can be imaged. It is of high importance to identify the cellular and/or viral target genes in other to elucidate the function of the viral microRNAs. To understand the oncogenic ability of EBNA1 and the EBERs, either alone or together with a c-myc gene activated, transgenic models have not yet been fully experimented on. For one to rule out the position effects of the transgene and activate c-myc candidate genes in germinal center B cells directly, one must use a conditionally inducible (as well as conditionally reversible) transgenic knock-in models in mice.

The discovery of the novel form of Wp latency in BL cells in vivo is a critical step forward regarding the role of EBV in BL. Now, it is of high importance to correlate the different subtypes of viral latency, their prognosis and responses to chemotherapy. If any subtype of viral latency surely correlates with the clinical presentation, this will be a definitive proof that EBV is relevance in BL development in vivo.

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