Review Article

Reframing Burkitt lymphoma: virology not epidemiology defines clinical variants

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Abstract: In 1964, Epstein-Barr virus (EBV) was identified in a biopsy from a patient with Burkitt lymphoma (BL) launching a new field of study into this ubiquitous human virus. Almost 60 years later, insights into the role of EBV in lymphomagenesis are still emerging. While all BL carry the hallmark c-myc translocation, the epidemiologic classification of BL (e.g., endemic, sporadic or immunodeficiency-associated) has traditionally been used to define BL clinical variants. However, recent studies using molecular methods to characterize the transcriptional and genetic landscape of BL have identified several unique features are observed that distinguish EBV+ BL including a high level of activation induced deaminase mutation load, evidence of antigen selection in the B cell receptor, and a decreased mutation frequency of TCF3/ID3, all found predominantly in EBV+ compared to EBV– BL. In this review, the focus will be on summarizing recent studies that have done in depth characterization of genetic and transcriptional profiles of BL, describing the differences and similarities of EBV+ and EBV– BL, and what they reveal about the etiology of BL. The new studies put forth a compelling argument that the association with EBV should be the defining etiologic feature of clinical variants of BL. This reframing of BL has important implications for therapeutic interventions for BL that distinguish the EBV+ from the EBV– lymphomas.

Keywords: Epstein-Barr virus (EBV); lymphoma; Burkitt lymphoma (BL); viral-associated malignancy

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History of the discovery of Burkitt lymphoma (BL)

In 1958, Denis Burkitt described the cancer that is now known as BL (1). Although at first thought to be a sarcoma, BL was subsequently identified as a non-Hodgkin B cell lymphoma. The cancer typically presents extranodally and it was the unique presentation in the jaws of children that initially caught Burkitt's attention. The finding that BL was restricted geographically, led to initial speculation that the tumor was caused by a mosquito borne virus (2,3). Denis Burkitt presented his observations of the tumor at Middlesex Hospital in London. In the audience was Tony Epstein who, intrigued by the idea of an infectious etiology of the cancer, initiated a collaboration with Burkitt. This ultimately led to the identification of the virus, Epstein-Barr virus (EBV) (4), the first virus shown to be associated with cancer in humans. Since these initial discoveries, research on the role of EBV and BL continues to contribute to our understanding of oncogenesis and the role of viruses in driving malignancy.

Epidemiology of BL

Three clinical variants of BL have been described based on the epidemiology of the cancer: endemic, sporadic and immunodeficiency-associated (ID). The most common, and the variant initially described by Burkitt, is the endemic form of BL. Endemic BL (eBL) is a pediatric cancer with a peak incidence between 6–8 years of age and a predominance in males (5,6). eBL is found in regions of the world where malaria transmission is year-round,

predominantly sub-Saharan Africa and Papua New Guinea (6-9). eBL presents extranodally, frequently in the jaw in younger children and abdominally in older children (10). Recent studies indicate a changing pattern of presentation with less tumors occurring in the jaw than historically reported (11). EBV is detected in ~95% of cases (12,13).

In contrast to eBL, cases of sporadic BL (sBL) occur throughout the world. It is a rare malignancy and can occur in both children, young adults as well as the elderly (14,15). sBL represents ~50% of childhood lymphomas but less than 3% of all lymphomas in USA and Western Europe (16). The incidence of sBL in US children was reported to be 2.5 cases per million person-years (17). In contrast to eBL, EBV is detected in only 10–30% of sBL (18,19). In one study, 38% of pediatric sBL were found to be EBV-positive (20). sBL, like eBL, also occurs more frequently in males, typically presents within the abdominal region and is found in lymph nodes as well as extranodally (19).

A third subtype of BL emerged along with the HIV epidemic, HIV-associated BL (also called AIDS-related and more recently defined as ID-BL). HIV-associated BL occurs early in HIV infection and before $CD4^+$ T cell numbers drop (21,22). The incidence of HIV-associated BL has remained stable in the US since the introduction of combination antiretroviral therapy for HIV (23). This form of BL has 20–40% of cases that are EBV positive (24). However, the frequency of EBV+ tumors has been reported to be as high as 71% in a case series from Brazil (25). There are also a few case reports describing the occurrence of BL in post-transplant immunodeficient patients but this cancer is not common in this setting (26-29).

A different epidemiologic pattern of BL is found in South America where EBV is detected in approximately half of the cases of all ages (25,30-32). Some studies provided comparison of EBV positivity in BL occurring in children <5 years to children 5–16 years (33,34). Only children less than 5 years of age are consistently EBV+. This is in sharp contrast with eBL where there is no age dependent segregation of EBV positivity in children (20). Interestingly, the prevalence of EBV in BL varies between different regions within Brazil with regions in the North showing a higher frequency of EBV+ BL (25).

The variable association of the BL epidemiologic subtypes with EBV presents a challenge to our understanding of the etiology of this malignancy. Some have argued that because EBV is not consistently detected in different BL subtypes, EBV plays a non-pathogenetic role (35,36). However, as will be reviewed below, an argument can be made for distinguishing BL based on the presence or absence of EBV, not on the epidemiology of the tumor (e.g., sporadic *vs.* endemic). This has important implications for understanding the etiopathogenesis of the different BL clinical subtypes.

Pathology of BL

Part of the challenge in determining whether the endemic and sporadic forms of BL are distinct entities is the consistent histologic description of these tumors regardless of their epidemiologic origins. Dennis Wright was the first to describe the so-called "starry sky" appearance that is readily observed in cytologic preparations (37). This feature is due to the presence of a high mitotic index, marked apoptosis, and presence of tingible body macrophages. According to the WHO classification, BL are composed of monomorphic $CD19^+CD20^+$ B cells with basophilic cytoplasm (19), commonly IgM^+ (38,39) and a Ki-67 score of ≥95% (19). B cell lineage markers indicative of centroblasts are seen (e.g., CD10, BCL6, $CD38^{bright}$) (38,40) and germinal center gene expression program are also found (41) consistent with BL derived from centroblasts. Gene expression profiling of the different BL subtypes identified a common transcriptional program that is distinct from other non-Hodgkin B-cell lymphomas such as diffuse large B-cell lymphoma and with a profile similar to a germinal center B-cell origin (41-43). This molecular definition of BL, while important for understanding etiopathogenesis and development of new therapeutic approaches, is not feasible for routine diagnostic purposes.

All BL express high levels of MYC and greater than 90% have the characteristic translocation of the *MYC* oncogene (8q24) onto the immunoglobulin heavy (IgH) (14q34) in the majority of cases (>85%) [reviewed in (44)]. Infrequently, *MYC* translocates to the immunoglobulin light chain κ (2p12) or λ (22q11) locus (45). The translocation of *MYC* near immunoglobulin regulatory regions results in constitutive expression of MYC. *MYC* transcription is driven from the translocated allele (44,46). The chromosomal break points in both *MYC* and *IgH* vary between sBL and eBL (20) which argues for a different etiologic driver. The *MYC* translocation resulting in constitutive MYC expression is thought to be a key pathogenetic event leading to the emergence of a malignant clone (47).

The role of EBV

Despite almost 60 years since the discovery of EBV in a BL tumor cell, there are still many unsolved questions as to how EBV contributes to BL oncogenesis. The viral genome is detected in the majority of eBL cases (12,19). Subsequent analysis of EBV genomes in the tumor cells showed that the viral genome was clonal indicative that EBV infection preceeded the malignant transformation event (48). In a seminal prospective study in Uganda in the 1970's, antibodies to EBV viral capsid antigen (VCA) were increased significantly prior to the emergence of the tumor providing further evidence of EBV's causal role (49). Loss of the EBV genome from BL cell lines results in apoptotic cell death (50,51). In addition, EBV encodes several latent proteins [Epstein-Barr nuclear antigen (EBNA)-1, -2, -3A, -3C and latent membrane protein (LMP)-1] that are essential for B-cell transformation [reviewed in (52)].

One of the paradoxes of determining EBV's role in BL oncogenesis is the fact that only one EBV latent protein, EBNA-1, is consistently expressed in BL (53). Studies to examine the transforming capacity of EBNA-1 have yielded differing results. Wilson generated a transgenic mouse that expressed EBNA1 which resulted in B cell lymphomas (54). However, Kang *et al.*, was not able to reproduce this result (55). It should be noted that different mouse strains and different constructs for generation of EBNA-1 transgenic mice were used in these two studies. Inhibition of EBNA-1 in BL cell lines results in apoptosis (50,55). Consistent with this, Holowaty showed that EBNA-1 binds to USP7 (also called HAUSP), a deubiquitinase. USP7 binds to p53 and mdm2, stabilizing the proteins. Binding of EBNA-1 to USP7 destabilizes p53 potentially abrogating apoptotic responses (56). Of note, USP7 is mutated in EBV+ BL (39).

In addition to EBNA-1, the RNA-pol III non-translated RNAs termed EBV-encoded small RNAs (EBER)-1 and EBER-2 are also consistently expressed in BL (57,58) as well as all latently infected cells. Because of their high level of expression, the EBERs are readily detected by *in situ* hybridization and thus useful for identifying EBV+ cells in biopsies. Their functional role in EBV+ BL remains controversial. Takada and colleagues used an EBV+ BL cell line, termed Akata, that over time lost the EBV episome. They were able to show that introduction of EBER-1 restored resistance to apoptosis in this line via induction of BCL-2 (59). While this is an important study, it also highlights the challenge with addressing requirements for EBV-encoded RNA or EBV latent proteins in malignant transformation by using cell lines which are typically derived from BL biopsies and thus, not representative of a pre-malignant state where EBV is most likely to contribute to oncogenesis.

EBV-encoded BART miRNAs are also detected in EBV+ BL (57,60-62). The presence of the BART miRNAs in EBV+ BL was associated with a different transcriptional program (63) pointing to a possible oncogenic role. Forced loss of the EBV episome followed by expression of BART miRNAs rescues the cells from apoptosis via inactivation of CASP3 (64). Further evidence of an important role for miRNAs in BL comes from a study by Mundo *et al.* (65) where they were able to detect EBV miRNA in EBER-negative BL cells.

Other EBV latent and lytic transcripts and/or proteins have been detected in BL (57,58,66) but detection of these other viral transcripts is sporadic, not in the majority of tumor cells and the potential role for expression of these additional EBV transcripts in oncogenesis is not clear. There is one study that shows that detection of the immediate early protein, BZLF1 (also called ZEBRA) correlated with improved response to treatment (67). A subset of BL was identified that have a deletion of EBNA-2 gene and but express EBNA-3C (68) suggesting that EBNA-2, a MYC antagonist, needs to be downregulated either through transcriptional repression or through deletion.

A common theme emerges from a number of studies suggests that a prime role for EBV is to disarm apoptotic triggers in B-cells such as the over-expression of MYC (69). The corollary idea is that following disarmament of apoptosis, the requirement for expression of any EBV gene is unnecessary (36,70).

For the EBV– BL subtype, a hit and run mechanism has been proposed where EBV plays an initiating role in oncogenesis but the viral genome is lost (70,71). Two recent studies identified "traces" of EBV infection in BL primary tumors where they detected EBV miRNA but not EBER (65,72). This raises the intriguing possibility that EBV– BL are actually derived from EBV-infected B cells which because of the absence of EBERs, a potential link with EBV can be missed. Analysis of cellular mutations in EBV– BL also has led to the hypothesis that EBV can be lost because

compensatory mutations have occurred that substitute for the functions of EBV proteins (70). However, other studies that have identified unique gene expression profiles (GEPs) between EBV+ and EBV– BL (41) and evidence of ongoing somatic hypermutation in EBV+ BL but not in EBV– BL (39,73) which argue for different pathogenetic mechanisms driving the emergence of EBV+ and EBV– BL.

One possibility that has been addressed by a number of groups is whether there is a particular strain or variant of EBV associated with BL that had more oncogenic potential. However, the results have not been consistent and this question remains open. For example, Bhatia and colleagues classified five EBNA-1 subtypes and proposed that the V-leu subtype was more common in both BL as compared to healthy controls (74). However, a subsequent study by Rickinson and colleagues found no evidence of a selection of a particular EBNA-1 subtype in BL cases compared to controls (75). Similarly, Moormann and colleagues reported no evidence of a promoter variant, the ZpV3, in BL cases versus controls (76), while Kenney and colleagues did (77). Conversely, Grande *et al.* found no evidence of a bias towards EBV type 1 predominating in eBL (39) while Kaymaz *et al.* did (78). Earlier studies on HIV-associated and eBL found equal distribution of EBV types 1 and 2 (79) while BL cases in Brazil had a predominance of EBV type 1 (25). Unique variants of the LMP-1 have also been reported in eBL compared to controls (80,81). An important challenge in addressing this critical question is identifying the appropriate control population as a reference for the EBV genome strain(s) circulating within a population.

Because both strains of EBV are found in BL, an interesting question was whether there were cellular mutation differences in BL carrying either EBV type 1 or type 2. In one study, EBV type 2+ BL had less mutations in key genes compared to EBV type 1 (73,78). In contrast, Grande *et al.* (39) did not find genes that were differentially mutated in BL carrying either EBV type 1 and type 2 BL. Further studies on larger panels of BL tumors are required to resolve these discrepant results. It is possible that variations in EBV type between different geographic regions within sub-Saharan Africa could also account for these differences.

Activation-induced cytidine deaminase (AID) and BL

When the *MYC* translocation was first identified, there was speculation that it was mediated by the VDJ B cell recombinase used in the recombination of the variable and joining regions of the immunoglobulin genes (44). However, in 2008, Robbiani and colleagues provided the first evidence that the enzyme, activation induced cytidine deaminase (AID) (also called AICDA), was a cause of the *MYC* translocation (82). AID is the critical enzyme for somatic hypermutation and class switch recombination of immunoglobulin genes, key features in the generation of adaptive humoral immunity [reviewed in (83)]. AID induces point mutations by deaminating cytidine to uracil. Because of this, it is easy to identify cellular mutations as being caused by AID. AID can also induce DNA breaks in the immunoglobulin genes.

Because of the potential danger to the cell of having an enzyme capable of modifying the genome, AID is regulated not only at the transcriptional level, but also through translational, post-translational and sub-cellular localization (84). AID is also tightly regulated during B cell differentiation and expressed only in germinal center B cells in health (85). Evidence that both EBV and *Plasmodium falciparum*, etiologic co-factors in eBL, can aberrantly induce AID comes from both animal and cell culture models. *Plasmodium* infection alone can induce aberrant AID expression in B cells outside of the germinal center reaction in a mouse model of *Plasmodium* (86). Extracts from *P. falciparum* infected red blood cells were also shown to induce AID expression (RNA and protein) in tonsil B cells (87). More direct evidence of *Plasmodium* comes from a study by Robbiani *et al.* (88) where they repeatedly infected p53 deficient mice with *Plasmodium chabaudi* and induced lymphomas that had the characteristic *MYC* translocation on the IgH. Using an AID knockout mouse, they then showed that the capacity to induce a translocation was dependent on AID. Overexpression of MYC in normal B cells results in stress response apoptosis mediated by p53, ATM and p19 (89) suggesting that even if AID induces off-target translocation of *MYC* in normal cells, these cells will likely undergo apoptosis. Of note in the Robbiani study, no tumors occurred in mice in the absence of p53 implying that abrogation of apoptotic pathways is critical to emergence of the malignant cell in BL.

The story with EBV and AID activation is a bit more complicated. EBV infection of B cells *ex vivo* induces AID activity (90). Consistent with this, both the EBV LMP-1 as well as the EBNA-3C induce AID expression (91-93).

AID was functional in these experiments as evidenced by accumulation of point mutations (91) as well as induction of T-cell independent class switching (92). LMP-1 induction of AID was indirect through upregulation of Egr-1 transcription factor (93). EBNA-3C was shown to bind directly to regulatory elements in the *AICDA* gene that encodes AID (91). However, overexpression of EBNA-2 inhibited AID expression (94) potentially counteracting LMP-1 and EBNA-3C induced AID activity. Moreover, EBV+ BL do not typically express LMP-1, EBNA-3C or EBNA-2 so if there is an EBV mediated effect on AID it preceedes oncogenesis.

Three studies in humans point to dysregulated AID expression in populations at risk for BL. First, Torgbor *et al.* (87) found AID frequently expressed in the tonsil lymphocytes of children from a malaria endemic region of Ghana but not in tonsil lymphocytes from children living in the US. In a study based in Kenya, elevated AID expression was correlated with peripheral EBV loads in children with repeated exposure to malaria (95). Elevated expression of AID in peripheral blood lymphocytes was detected prior to the emergence of BL in HIV+ patients (90) suggesting that dysregulation of AID is an early step prior to the *MYC* translocation. This is critical point as it leads to a hypothesis that chronic immune activation, regardless of inciting agent (e.g., viral or parasite) can drive the *MYC* translocation (96).

More recently, in a landmark paper, Staudt and colleagues sequenced DNA from over 100 EBV+ and EBV– BL biopsies and through analysis of both genome sequences and transcriptome data found that the genome wide mutational load was increased significantly in EBV+ BL compared to EBV– BL regardless of the epidemiology of the tumor (39). They hypothesized that the increased mutations were due to increased AID activity based on analysis of the point mutations that clearly have the mark of the cytidine deaminase. AID was also more highly expressed in eBL than in sBL. A subsequent study by Panea *et al.* (73) also found that EBV+ eBL had a mutational burden indicative of AID activity.

Other co-factors

When EBV was first discovered, it was thought (and hoped) that this would be the answer to understanding BL and possibly preventing BL. Unfortunately, EBV is a necessary but not sufficient cause of the malignant transformation that occurs in the EBV+ BL. As observed by Burkitt and colleagues early on, there was a clear epidemiologic link between cases of BL and endemic malaria transmission (97) and confirmed in later studies (7,98). However, it wasn't until the 2000's that we had a causal link both in the case control studies of Newton and colleagues in Malawi and Uganda where children with eBL had higher titers of anti-malaria antibodies as compared to controls (99,100). In addition, Robbiani by repeatedly infecting $p53^{-/-}$ mice with *P. chaubadi*, showed AID-dependent *MYC* translocated lymphoma similar to BL in humans (88). Combined, these studies provide the strongest evidence for a causal role of malaria in BL.

Within the context of both *P. falciparum* malaria and HIV, there is also a possible role for immunosuppression of EBV-specific responses. For example, Whittle *et al.* (101) demonstrated that peripheral blood lymphocyte (PBL) isolated from adult patients with acute malaria were unable to control outgrowth of EBV-transformed cells in a standard but relatively crude regression assay to assess EBV-specific T cell function. Moss *et al.* (102) demonstrated that healthy adults living in malaria holoendemic regions of Papua New Guinea had impaired EBV-specific T cells responses using the same regression assay. In children experiencing an episode of acute malaria, spontaneous outgrowth of EBV-transformed B cells *ex vivo* occurred at greater frequency (103). More recent studies show loss of EBV specific cytotoxic T lymphocyte (CTL) responses to lytic antigens in children living in a malaria holoendemic region (104) and a specific loss of IFNg CTL responses to EBNA-1 in eBL patients (105). A model put forward by Liu *et al.* (106) proposes that repeated infections with one pathogen (for example, *Plasmodium*) weakens the total CTL memory, such that established CTL memory to a different pathogen (such as EBV) will be diminished and ultimately collapse. This model could explain loss of EBV-immunity that has been reported in the above studies and could also account for how chronic antigen stimulation from not only *P. falciparum* but also other pathogens such as HIV could contribute to the emergence of BL.

If *P. falciparum* malaria and EBV act in concert to drive eBL, what are the factors that drive the other clinical variants of BL? One possibility is that factors that induce chronic activation of B cells and aberrant AID expression could trigger the MYC translocation. This model relies on B cell receptor (BCR) stimulation through extrinsic

activation. Evidence of antigen selection of BCR in BL in both mouse models (107) and in humans (108) is found and suggests that other chronic infections including HIV could trigger lymphomagenesis (41,109). In contrast, analysis of BCR signaling in sBL is more indicative of mutations that allow tonic BCR signaling and not necessarily antigen selected (107,110). Because of the relatively low incidence of sBL, understanding the etiology becomes more challenging and has not been extensively explored. But it is clear that for all variants of BL, a *MYC* translocation and evasion of apoptosis are critical steps on the oncogenic pathway.

Defining BL based on the presence or absence of EBV

With the advent of more comprehensive "omic" techniques to evaluate the mutations in the cellular genome and define transcriptional profiles, these techniques have now been applied by several groups to identify molecular pathways that are disrupted in BL [(110-113), reviewed in (36)]. Common pathways dysregulated in BL include tonic B-cell receptor signaling, phosphoinositide 3-kinase (PI3K) pathway, and cyclin D3/CDK6 as well as mutations in the tumor suppressor, ID3, diminishing its function. Activating mutations in TCF3, a negative regulator of ID3 are also observed pointing to the critical importance of this pathway in driving cell proliferation. Other common mutations in BL include *ARID1A* and *SMARCA4*, part of the SWI/SNF family and involved in nucleosome remodeling. In addition, mutations are found in *MCL1*, *FBX011*, *DDX3X*, *CCND3* as well as *TP53* and *MYC*.

A challenge in compiling a comprehensive picture of the genomic landscape of BL is that while translocation of *MYC* and subsequent overexpression of MYC is the primary pathogenetic event, cellular mutations (e.g., deletions, amplifications, point mutations) evolve independently to target different cellular pathways (e.g., proliferation, apoptosis, immune escape). Genotype-phenotype correlations along with clinical correlations are needed to define the spectrum of mutations in BL and move into the field of precision medicine. And while, as noted above, certain patterns are emerging that shed light on the genetic basis of BL, it has becoming increasingly clear that the presence or absence of EBV in the lymphoma is the feature that defines other molecular differences (39). With this point in mind, it useful to go back and look at the reported differences in studies that compared eBL (almost always EBV+) and sBL (almost always EBV–) through the lens that EBV is the defining feature. *Table 1* summarizes these studies and with this information a clear picture emerges of the molecular differences between EBV+ and EBV– BL.

The first key molecular difference in eBL *vs.* sBL was the breakpoint differences in the MYC translocation. In eBL, the translocation occurs 5' of the MYC coding region while in sBL, the translocation typically occurs within the 1st intron or exon (20,117,118). Bellan and colleagues analyzed eBL, sBL and ID-BL for rearranged immunoglobulin heavy chain (V_H) genes and compared them to germline V_H segments (114). They found that the EBV+ BL regardless of epidemiologic origin, had more somatic mutations and evidence for antigen selection while the EBV– BL had only a small number of somatic mutations. Follow-up studies using next-generation sequencing (NGS) of Ig genes found intraclonal diversity supports a model for antigen-driven selection of BCRs in eBL (108). A subsequent GEP comparing eBL to sBL identified both similarities such that all BL were distinct from other non-Hodgkin lymphoma but also differences with 74 unique genes expressed in eBL but not sBL (41). An additional study evaluated EBV+ and EBV– ID-BL and again found differences, notably in 19 cellular miRNAs that were upregulated in the EBV+ BL compared to the EBV– BL (61). Both eBL and sBL had mutations in the forkhead box subtype (FOXO) transcription factor but there were differences in the presence of a mutation in the AKT recognition motif with T24 mutation common in sBL while the S22 was common in eBL (115). And as noted earlier both Grande and Panea identified evidence of AID mutation activity in EBV+ but it was not as extensive as in EBV– BL (39,73). In addition, Abate *et al.* (58) found evidence of decreased mutations in *MYC*, *ID3*, *TCF3* and *TP53* in EBV+ BL compared to EBV– BL while an increase in mutations in *ARID1A*, *RHOA* and *CCNF*. In addition, they also reported that the TCF3 target genes are more activated in EBV– BL (58). Interestingly, in EBV+ BL, noncoding mutations were in regulatory regions and likely due to AID activity (39). In this same study, they also found that mutations in apoptotic pathways defined EBV– BL but not EBV+ BL consistent with a hypothesis that one of EBV's role in etiopathogenesis of BL is to abrogate apoptotic pathways.

An analysis of human miRNA in BL subtypes while finding differences in 38 miRNAs between BL and diffuse

Table 1 Comparison of molecular differences between EBV+ and EBV– BL[#]

Study	Analysis/sample type*	EBV+	EBV–
Bellan *et al.* (114)	Mutation rates in V_H	6.1 average mutation frequency in V_H	1.4 average mutation frequency in V_H
	Sequence analysis of CDR2 region for evidence of antigen selection	11/18 evidence antigen selection	0/13 evidence of antigen selection
Piccaluga *et al.* (41)	Gene expression profile (GEP)	74 unique genes including BCR, TNFα/NF-κB, interleukin-dependent cascades	–
	eBL *vs.* sBL	↑miRNA	–
	EBV+ *vs.* EBV– for miRNA	↑*RBL12* network genes	–
		GC gene profile	GC gene profile
Navari *et al.* (61)	GEP miRNA profile	Enrichment for metabolic processes	↓27 miRNA
	EBV+ *vs.* EBV– ID-BL		↑has-miR-142-5p
Zhou *et al.* (115)	Sanger sequencing of eBL and sBL, NGS of sBL	Mutations in *FOX01*	Mutations in *FOX01*
	eBL 100% EBV+	Mutations in S22 and distal to AKT recognition	Mutations in T24 phosphorylation site
Amato *et al.* (108)	RNA seq/NGS sequencing of Ig genes	↓Mutation frequency of TCF3/ID3	↑Mutation frequency of TCF3/ID3
	eBL *vs.* sBL	Intraclonal diversity	
Grande *et al.* (39)	Whole genome sequencing, RNA-seq, miRNA-sea	↑Mutation load per genome	↓Mutation load
		↑Proportion of AID associated mutations	↑TP53 mutations
		↑AID expression	–
		Mutations in *SIN3A*, *USP7*, *CHD8*	–
		↓Driver mutations esp. in apoptosis genes	–
		↑Noncoding mutations	↑Coding mutations
Giulino-Roth *et al.* (113)	NGS	Less likely to have genetic alterations	More likely to have multiple genetic alterations
	Pediatric BL		
Abate *et al.* (58)	RNA seq	↓Mutations in *MYC*, *ID3*, *TCF3*, *TP53*, *DDX3X*, *CCND3*	Mutations in MYC, ID3, TCF3, TP53
	eBL *vs.* sBL	↑Mutations in *ARID1A*, *RHOA*, *CCNF*	TCF3 pathway more activated
	TCF pathway analysis on EBV+ *vs.* EBV–		

Table 1 (*continued*)

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Study	Analysis/sample type*	EBV+	EBV–
Panea *et al.* (73)	Whole genome sequencing, RNA seq	↑Mutation load per genome	↓Mutation load
		↑Proportion of AID associated mutations	
		↑Mutations in *BCL7A*, *BCL6*	
		↓Mutations in *DNMT1*, *SNTB2*, *CTCF*	
Kaymaz *et al.* (78)	RNAseq, gene set enrichment	1,658 diff expressed genes	–
		↓*PTEN* suppressed	
		↑DNA replication, mismatch repair, cell cycle regulation	
Lenze *et al.* (116)	miRNA microarray	↑10/18 targets of miR-127	–
	eBL *vs.* sBL	↑hsa-miR-10b, -216b, -499-3p	↑hsa-miR-191, -374a, -193-5p

AID, activation-induced cytidine deaminase; BCR, B cell receptor; BL, Burkitt lymphoma; eBL, endemic Burkitt lymphoma; EBV, Epstein-Barr virus; GEP, gene expression profile; ID-BL, immunodeficiency-associated Burkitt lymphoma; GC, germinal center; NGS, next-generation sequencing; sBL, sporadic Burkitt lymphoma.

large B-cell lymphoma, also identified 6 miRNAs that were different between eBL and sBL (116). A subsequent study confirmed this observation that the differences were between EBV+ and EBV– BL and also found 10/18 targets of has miR-127 that were upregulated in EBV+ BL (41).

Since the discovery of EBV, the question has remained whether EBV is the driver or passenger on the road to malignant transformation of B-cells in BL. The theme emerging from the molecular analysis of BL is that the presence or absence of EBV is a defining feature of the clinical variant regardless of the epidemiology of the tumor. And that the convergence of similar pathology of clinical variants now shows that there are molecularly distinct EBV+ and EBV– entities. With this knowledge, we are still challenged to understand where in the B-cell differentiation pathway does EBV induce premalignant changes and increase susceptibility to malignant transformation.

In *Figure 1*, a model of etiologic pathways of EBV+ and EBV– BL is presented. In this model and consistent with pathologic findings, BL starts as a germinal center B cell, likely a centroblast. Both pathways posit 4 key features: (I) suppression of apoptosis, (II) activation of AID, (III) MYC translocation and (IV) accumulation of additional mutations that enhance cell proliferation/survival/growth. Where they differ is that EBV likely induces AID and accumulation of point mutations that distinguish the EBV+ and EBV– BL (39). Another key difference is the role of EBV in suppressing apoptotic pathways for EBV+ BL while mutations in ID3/TCF3/p53 play that role in EBV– BL (58). The steps in these two pathways remain to be fully elucidated.

Conclusions

Guy de-Thé once called BL the Rosetta Stone of cancer (120). Through the study of this cancer first identified in Uganda, scientists have uncovered the first human cancer virus, developed the first human B cell line, identified the first human oncogene, and developed new models for cancer treatment that relied on chemotherapy alone. As we move further into the 21st century, BL is still serving as our guide as we uncover the mechanisms of oncogenesis and the differences in etiopathogenesis of EBV+ compared to EBV– BL.

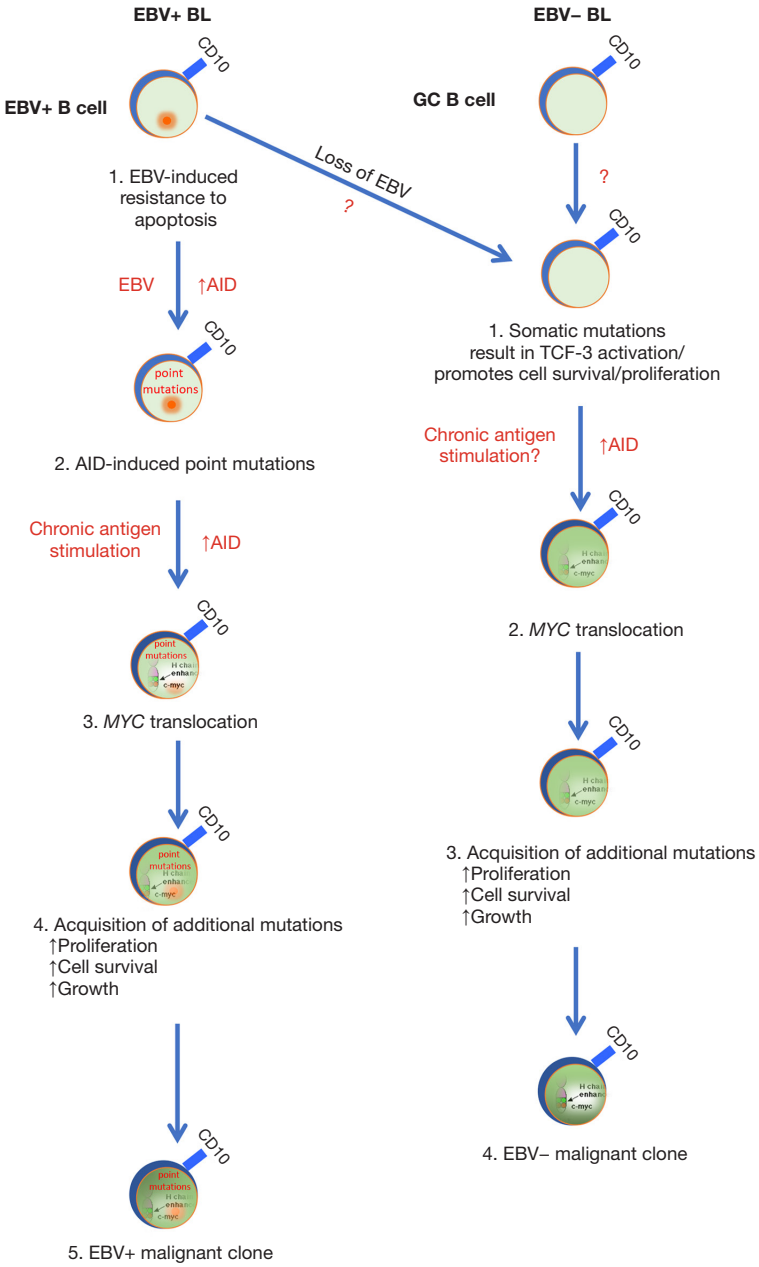

Figure 1 Model for etiology of EBV+ and EBV– BL. For EBV+ BL, EBV infection of the B-cell through epigenetic modifications results in methylation of tumor suppressor Bim, a pro-apoptotic gene, and renders the cell resistant to pro-apoptotic signals (119). The red dot indicates EBV; the Ig-MYC translocation and the darker nucleus indicate acquisition of mutations. EBV proteins can induce AID resulting in accumulation of point mutations in the genome. Chronic antigenic stimulation such as occurs in areas where malaria infection occurs repeatedly throughout childhood results in further induction of AID and the hallmark MYC translocation onto the Ig heavy chain enhancer. Additional mutations in oncogenes arise that result in the emergence of a malignant clone. It is likely that these additional mutations occur later in the oncogenic pathway as there is not a consistent mutational pattern. The triggers for the original mutations that occur in EBV– BL are unknown. Shown is a possible link with loss of the EBV episome (termed a hit and run) that could be the first step in some cases of BL. The transcription factor, TCF3 is activated through mutations and the upregulation of TCF3 is found in most cases of BL (cite Schmitz/ Staudt). In this model, TCF3 activation is indicated as an early step in oncogenesis prior to MYC translocation as the upregulation of TCF3 would alter transcriptional profile of the pre-malignant cell to prevent apoptosis induced by over-expression of MYC. EBV, Epstein-Barr virus; BL, Burkitt lymphoma; AID, activation-induced cytidine deaminase; GC, germinal center.

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