VIRUSES AND LYMPHOMAS

Epstein–Barr virus and Burkitt lymphoma

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Burkitt lymphoma (BL) is an aggressive B-cell malignancy with endemic, sporadic and immunodeficiency-associated variants. It has been known for many years that the fundamental transforming event in BL is the translocation of the *MYC* gene, and the events that bring about this translocation and those that allow cells to survive with the constitutive expression of *MYC* have been the subject of intense investigation. Epstein–Barr virus (EBV) infection, malaria, immunodeficiency and spontaneous, somatic mutation can all contribute to the origin and maintenance of this cancer and their mechanisms are the subject of this review.

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Burkitt lymphoma (BL) can be classified into three forms which differ in geographic distribution and Epstein–Barr virus (EBV) association: endemic (eBL), sporadic (sBL) and HIV-associated BL (table 1). The hallmark of all BL tumours is the translocation between the *MYC* gene and one of the immunoglobulin (Ig) heavy or light chain loci. There is a low background incidence of BL worldwide (sBL), which is rarely associated with EBV and accounts for 1–2% of adult lymphoma in Western Europe and America, but eBL is associated with (EBV) in over 95% of cases and is predominant in the equatorial belt of Africa and other parts of the world where malaria is hyperendemic.[1–4] BLs that display an intermediate association with EBV have also been documented in Egypt and Brazil, where up to 87% of tumours are EBV positive[5–7] and BL occurs in HIV carriers, where tumours can develop prior to the severe immunosuppression coincident with the onset of AIDS. Approximately 30% of such AIDS-associated tumours are EBV-positive.[8 9]

Endemic EBV-associated BL has an incidence of 5–10/100 000 children and accounts for up to 74% of childhood malignancies in the African equatorial belt.[3] In contrast to sBL, which most frequently involves tumours of the abdomen,[4] eBL often presents in the jaw or kidneys[10 11] but may also occur in the abdomen, ovaries, facial bones and other extranodal sites.[1] The cancer has one of the highest cell proliferation rates of any human tumour (doubling time of tumour 24–48 h).[12]

Histologically, BL cells are monomorphic medium sized cells with round nuclei, a number of nucleoli and abundant cytoplasm. Tumours display a "starry sky" pattern owing to the presence of high numbers of macrophages, which phagocytose apoptotic debris.[1] BL tumour cells usually express IgM,[13–15] B-cell markers such as CD19, CD20 and CD22 and markers of germinal centre (GC) centroblasts such as CD10, *BCL6*[4] and the human germinal centre-associated lymphoma (HGAL) protein.[16]

It remains to be firmly established whether eBL originates from a GC-derived or memory B cell.[17–22] The cell surface phenotype of BL tumour cells reflects a GC origin but the site of tumour growth is frequently the jaw or ovary, neither of which normally contain GCs. However, the tumour cells have undergone hypermutation,[21 23] a feature of the GC reaction during B-cell activation and differentiation. Moreover, the breakpoint in the Ig gene to which *MYC* is transferred in eBL occurs at the V(D)J region, suggesting that translocation occurs during V(D)J recombination. The J segments flanking *MYC* translocated breakpoints typically exhibit deletions and/or additions of base pairs characteristic of normal Ig V(D)J segment rearrangement.[24 25] This is a process catalysed by B-cell specific V(D)J recombinase activating enzymes RAG-1/2 which are expressed in both pre-B cells and GC B cells.[26 27] In contrast, the chromosomal breakpoint in sBL and HIV-associated BL occurs most commonly in the class switch region,[28] but since both somatic hypermutation and class switching are events that are normally confined to GC B cells and GC centroblast markers are expressed on BL cells, the BL progenitor cells most likely arise from B cells subjected to chromosomal rearrangements in the GC.

There is some evidence that the cell of origin may be a post-GC or memory B cell re-entering the GC[18 22] and may differ in EBV-positive and negative tumours,[18] but whichever is the cell of origin, it is clear that GC involvement is critical to the pathogenesis of this disease both in terms of *MYC* translocation events and the contribution of co-factors such as EBV, malaria or HIV infection. For example, malaria and HIV infection have both been reported to activate B cells.[29–32] The greater the number of B cells activated and entering the GC reaction the greater the possibility that one cell may subsequently accumulate oncogenic mutations. Interestingly, the C1DR1α motif of the malarial parasite has been shown to drive B-cell proliferation and protect B cells from apoptosis.[32] Furthermore, HIV has been shown to induce the production of cytokines such as interleukin (IL)-6 and IL-10 that drive the proliferation of B cells.[33–36] The combination of malaria-mediated activation and enhanced survival of B cells plus EBV-driven proliferation of GC B cells may therefore help *MYC*/Ig translocation-positive B cells to survive, giving rise to a BL progenitor cell (fig 1).

THE ROLE OF MYC TRANSLOCATIONS IN BL PATHOGENESIS

A defining feature of BL is the reciprocal translocation between the *MYC* gene and one of the three immunoglobulin genes: the immunoglobulin

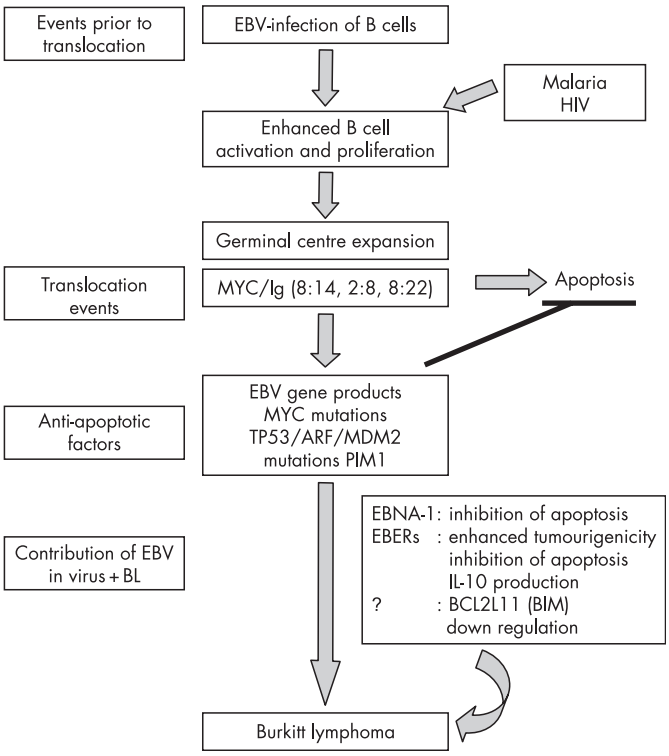

Figure 1 Pathogenesis of Burkitt lymphoma.

heavy chain gene (*IgH*, *IGH*), and the kappa (*IG*K) or lambda light chain (*IGL*) genes. In 80% of cases the t(8;14) translocation occurs with the *IGH* gene. The remaining 20% of cases are split between the translocations with the *IGK* and *IGL* (t(2;8) and t(8;22) respectively). Although *MYC* translocation can also occur in other human cancers such as diffuse large B-cell lymphoma[37] and multiple myeloma,[38] it is not thought to be the primary transforming event in these diseases.[39 40] Transgenic insertion of *MYC* into the *IgH* site resulted in B-cell and plasma cell neoplasms in mice.[41–43] Similar translocations have also been observed in the spontaneous cancers murine plasmacytoma and rat immunocytoma, with a predominance of *IGH* translocations in both cases.[44 45]

The *MYC* proto-oncogene plays a critical role in regulating cell proliferation, differentiation and apoptosis in a cell-type or context-dependent manner.[46] Its sequence and activities are widely conserved in evolution.[47–49] The transforming activity of MYC involves its activity as a sequence-specific transcriptional activator. Its C-terminal basic helix–loop–helix zipper domain facilitates binding to DNA sequences with the core consensus CACGTG (''E-boxes''),[50] requiring the association of its heterodimeric partner, Max.[51] MYC possesses an N-terminal transactivation domain through which it drives the expression of a large array of target genes,[52 53] the mutation of which results in loss of its activity as an oncogene.

The *MYC* gene comprises three exons. Exon 1 is non-coding but there are two promoters and regulatory sequences. Exons 2 and 3 contain the protein-coding sequence beginning on nucleotide 16 of exon 2.[54] Most *MYC* expression occurs from the P2 promoter (80–90% total MYC mRNA),[55] but *MYC* has a complex transcriptional and post-transcriptional regulation which acts to strictly limit the levels of MYC in the cell. It has a short-half life and is degraded by ubiquitin-mediated proteolysis driven first by phosphorylation of serine-62 followed by threonine-58, both modifications being activated by the Ras/MAP kinase/Akt pathways.[56 57]

The breakpoints in the translocated MYC gene occur at different positions in the different forms of BL. In sBL breakpoints are usually within exon 1 or intron 1, whereas the breakpoint in eBL is often at a great distance from the transcriptional start site.[58] These differences likely reflect distinct mechanisms of pathogenesis and the differentiation state of target cells in the development of sBL and eBL. However, in both cases, the coding region of the *MYC* gene is transferred intact. The breakpoint in the immunoglobulin gene to which *MYC* is transferred also differs in these two forms of BL.

Expression of *MYC* is normally under tight regulation during the cell cycle but once translocation occurs, expression is constitutive and deregulated, often reaching levels higher than in activated or EBV-infected B cells. The immunoglobulin enhancers at the adoptive locus appear to be the major deregulating factor on *MYC* expression, but the locations of breakpoints within *MYC* have also been correlated with expression levels of the gene product,[59] and *MYC* promoter elements can continue to modulate expression from the new site.[60–62] Transcription of translocated *MYC* occurs preferentially from the P1 promoter,[63 64] a shift driven by the immunoglobulin enhancers. The normal *MYC* allele is typically silent in BL,[65–67] so expression of *MYC* in these cells is derived solely from the deregulated allele.

Translocation of *MYC* and the immunoglobulin loci is believed to be aided by the presence of recombination switch sequences in *MYC* .[68 69] Interestingly, higher-order, spatial organization of B-cell DNA during interphase puts *MYC* and the immunoglobulin loci in close proximity, perhaps favouring reciprocal translocations.[70] Double, independent *MYC* translocations have been observed in murine plasmacytoma to both the *IGH* and *IGK* or *IGL* loci, further suggesting a non-random, reproducible mechanism for *MYC* transfer.[71 72]

Genetic translocation is not the only means of *MYC* deregulation. Mutations which increase the expression, activity and stability of *MYC* have also been reported.[73 74] These mutations are likely to occur after translocation of *MYC* to the Ig region where somatic hypermutation occurs in germinal centre B cells. Several mutations have been found in the regulatory regions of exon/intron 1 which block negative regulation of *MYC* expression.[75] Mutations in the *MYC* coding region have also been reported. For example, a commonly occurring mutation in threonine 58 prevents proteolytic degradation of MYC, thereby increasing turnover time of the protein in BL cells.[76]

ROLE OF OTHER GENETIC CHANGES IN SURVIVAL OF BL TUMOUR CELLS

A key aspect of MYC function in BL cells is the phenomenon of MYC-induced apoptosis. While MYC potently drives S phase progression in most somatic cells, cells normally undergo apoptosis when MYC levels exceed a ''safe'' threshold.[77] Overexpression of MYC in B cells causes induction of p53 or ARF, resulting in apoptosis.[78 79] In mouse cells a product of the *CDKN2A* (INK4a-ARF) locus, $p19^{ARF}$[80] stabilises p53 by associating with and antagonising MDM2,[81–83] a key negative regulator of p53.[84] High levels of MYC drive apoptosis by inducing $p19^{ARF}$ expression, resulting in an increase in apoptotic p53.[85] In human cells the equivalent (slightly smaller) ARF protein is $p14^{ARF}$.

Additional changes are therefore selected during the development of BL to counteract this apoptotic effect. The threonine 58 mutation mentioned above also blocks the ability of MYC to induce the expression of the apoptotic BCL-2 family member BIM. BIM interacts with the anti-apoptotic protein BCL-2, inhibiting its function and appears to be an important regulator

Table 1 Characteristic features of the different Burkitt lymphoma subtypes

	Endemic	Sporadic	HIV-associated
Distribution	Equatorial belt of Africa and Papua New Guinea	Worldwide	Worldwide
EBV association	98%	5–10%	30–40%
Co-factors	EBV, malaria infection	–	HIV infection
Incidence	5–10/100 000	0.01/100 000	Variable
MYC breakpoint	Often >1 kb upstream from 1st coding exon	Exon 1/intron 1 of *MYC* gene	Exon 1/intron 1 of *MYC* gene
Ig breakpoint	Joining (J) region, switch (S)μ in some cases	Sμ, Sα or J region	Sμ region
Progenitor cell	GC, late GC or memory B cell	GC B cell	GC, late GC or memory B cell
Frequent site of occurrence	Most frequently jaw. Abdomen, kidneys and ovaries may also be involved	Most frequently abdomen. Kidneys, bone marrow and ovaries may also be involved	Lymph nodes, abdomen, bone marrow, CNS

of apoptosis in these cells.[86] Mutations of the T58 site and related amino acids that prevent the phosphorylation of this residue represent an important means by which BL cells retain MYC-driven proliferation yet evade its apoptotic effects,[87] but the exact mechanism by which MYC activates BIM has yet to be described. Recent data shows that EBV-infected lines express lower levels of BIM than parental lines, suggesting that a latent EBV product blocks apoptosis by down-regulating the expression of BIM.[88 89]

Another means of evading MYC-driven apoptosis is by mutation of *TP53*, the gene encoding p53. It has long been known that cells lacking p53 and ARF activity are resistant to MYC-driven apoptosis.[90 91] Up to one third of BLs have acquired inactivating *TP53* mutations[92 93] and most BL cell lines have alterations in some part of the p53/ARF/MDM2 pathway.[94] Recently, the anti-apoptotic kinase, PIM-1, was reported to be hyperactive in Burkitt lymphoma, causing increased MDM2 levels in these cells, resulting in the destabilisation of p53.[95] Restoration of p53 activity in BL cell lines results in a decrease in tumourigenicity.[78] Interestingly, BL cells with inactivating *TP53* mutations appear to be devoid of *MYC* mutations.[87] These data suggest that once inactivating *TP53* mutations have occurred, there is no longer a requirement for further lesions in *MYC* to block apoptosis.

Mutations that disrupt the nuclear localisation signal of the RB-related gene, *RBL2* (RB2/p130) have also been reported in eBL, correlating with high levels of proliferation.[96 97] It was suggested that alterations in p130 may drive proliferation prior to translocation of the *MYC* gene.

ROLE OF EBV IN BL CELL SURVIVAL

The presence of EBV in GC cells that undergo a *MYC* translocation is also likely to aid cell survival. EBV is a ubiquitous gamma herpesvirus that establishes a seemingly harmless latent infection in B cells in over 95% of the human population, but is also involved in several types of cancer. The identification of clonal EBV genomes in all cells of tumours[98] indicates that the progenitor tumour cell was infected with EBV and supports the notion that the virus plays a role at an early stage of tumourigenesis. Moreover, antibodies to the EBV viral capsid antigen (VCA) are raised months or years prior to the development of disease and can correlate with disease burden.[99]

EBV can display three patterns of latent gene expression: latency I (latency programme), II (default programme) and III (growth programme). Latency III is characterised by expression of all the latent genes (EBNAs, LMPs and EBERS) and occurs on primary infection of B cells, where EBV clearly drives cell proliferation. In contrast, persistent infection in vivo is characterised by expression of EBNA-1 and LMP-2 plus the EBER RNAs.[100] eBL cells usually express only the EBNA-1 protein plus the EBERs (latency I), giving rise to debate as to how EBV may directly contribute to tumour growth. One report also detected LMP2A RNA.[101]

The restricted EBV latent gene expression profile[102] and reduced expression of MHC class I, transporter associated with antigen processing (TAP) molecules and the proteasome subunit LMP7 in tumour cells[103–105] help tumour cells to evade immune surveillance, but EBV gene products also seem to directly aid cell survival in the BL cells. Thus spontaneous loss of the EBV genome during passage of EBV-positive BL lines in vitro increases their sensitivity to apoptosis. Three per cent of EBV replicons are lost per cell per generation if they do not provide a survival advantage, yet expression of both EBNA-1 and EBERs is maintained in BL cells.[106]

In fact, roles for both EBNA-1 and the EBERs in the prevention of apoptosis and survival of BL cells have been reported. Early studies on transgenic mice expressing EBNA-1 in B cells suggested a predisposition to develop B cell tumours,[107] and experiments performed using a dominant negative EBNA-1 expressed from retroviral vectors demonstrated that inhibition of EBNA-1 reduced the survival of EBV-positive but not EBV-negative tumour cells in a dose-dependent manner. Cells in which EBNA-1 was inhibited displayed a four-fold increase in the level of apoptosis prior to loss of the EBV genome or changes in the level of the EBERs.[108]

In EBV-negative Akata BL cell the EBERs enhanced tumourigenicity and resistance to apoptosis,[109–111] increasing the growth of tumour cells in soft agar and significantly enhancing the tumourigenicity of EBV-negative BL cells in SCID mice.[110 111] EBERs (or EBER1 alone) have also been reported to bind to and inhibit the dsRNA-activated protein kinase, PKR[112–116] and consequently inhibit IFN-α induced apoptosis.[114] PKR regulates cellular stress and apoptotic pathways, but its reported role as a tumour suppressor led to suggestions that inhibition of its function by EBERs may play a role in tumourigenesis. The direct role of EBER-mediated PKR inhibition in mediating IFNα-induced apoptosis resistance has since been challenged,[111] casting doubt over a potential role for PKR in BL development under these conditions. Interestingly, EBERs have also been reported to be responsible for increased production of the B-cell growth factor, IL-10, in EBV-positive BL lines compared to EBV-negative BL lines.[117] IL-10 was shown to be present at higher levels in the tumour microenvironment of EBV-positive BL compared to EBV negative BL.[117 118] The recently discovered microRNAs in EBV do not appear to be expressed at high levels in BL cells,[119] but seem likely to be important in some other EBV-associated diseases such as nasopharyngeal carcinoma.

While EBNA-1 and the EBERs are generally thought to be the only EBV genes expressed in eBL, recent studies have found that a minor proportion of eBL tumours has a novel form of latency in which the EBNA-3A, 3B, 3C and LP latent genes are expressed in the absence of EBNA-2 and LMP-1 or 2.[103] These

tumours contain deletion mutants of EBV lacking the EBNA2 gene and this has led to the idea that EBNA2 is incompatible with the de-regulated *MYC* expression in BL cells, suggesting a selective pressure for loss of EBNA-2 expression (either latency I or deletion of EBNA2). Further investigation has demonstrated that eBL tumours may be comprised of tumour cells expressing variable patterns of EBV gene expression, each of which confer a different level of resistance to apoptosis.[120] In addition to the EBNA-2-deleted virus, EBNA-2^+ LMP-1^- clones and the previously described EBNA-1 only clones were identified. This finding supports early immunohistochemical studies in which the latent genes LMP-1 and EBNA-2 were identified in a proportion of eBL tumour cells.[121] Thus, EBNA-1, 3A, 3B, 3C and LP positive EBNA-2, LMP negative BL cells were the most resistant to apoptosis, while EBNA-2+, LMP1-negative BL cells displayed reduced but ''intermediate'' resistance. Latency I BL cells displayed the least resistance to apoptosis but afforded some level of protection compared to EBV-negative BL cells. Reports of eBL cases in Malawi in which EBNA-1, LMP1, LMP-2A, BZLF-1, EBERs and the BARTs were identified[122] suggest that EBV gene expression may be broader than previously thought, but these occasional exceptions can be seen as typical tumour heterogeneity and should not detract from our understanding of the usual EBNA1 and EBER only pattern of EBV gene expression in BL.

MALARIA AS A BL COFACTOR

The role of malarial infection in the pathogenesis of eBL is clear for the geographical co-incidence of the two diseases. It is generally thought that the association between malaria and BL arises from a combination of immunosuppression and B-cell activation. For example, cytotoxic T-cell mediated control over the outgrowth EBV-infected B cells is impaired during acute malaria infection,[123–125] and it has been found that peripheral EBV loads may be five times higher during acute malaria compared to levels observed during convalescence or in healthy individuals.[126] EBV loads are generally higher in areas of holoendemic malaria compared to areas where malaria is sporadic,[127] and show increased persistence in children with a history of severe rather than mild malaria,[128] possibly owing to higher viral reactivation.[129] eBL also develops at a later age in individuals who have migrated from malaria-free high altitude areas to lower, malaria-endemic areas.[130]

In support of these findings, it has recently been found that the malarial parasite *Plasmodium falciparum* can directly activate B cells via a cysteine-rich interdomain region 1α (C1DR1α) on the *P falciparum* erythrocyte membrane protein 1 (PfEMP1), which binds to surface Ig. The activation of B cells by C1DR1α and subsequent protection from apoptosis has been postulated to play a role in enhancing survival of GC B cells bearing oncogenic mutations.[32] In addition to the activation of B cells, it is possible that proliferation of B cells is enhanced by IL-10. Serum levels of this cytokine are raised in children suffering from acute *P falciparum* malaria compared to healthy controls.[131]

Protective immunity is only acquired following several years of exposure to the malarial parasite *P falciparum*,[132] and the intervening immunosuppression in malaria endemic areas may alter the regulation of EBV-positive B cells.[8 133] Immunosuppression is probably part of the mechanism of HIV-associated BL, but this can develop prior to the severe loss of immunity characteristic of AIDS, suggesting that severe immunosuppression is not a prerequisite for BL development. Additionally, EBV-associated tumours in post-transplant patients, in whom immunosuppression is severe, tend to display a latency III type EBV gene expression profile rather than the restricted pattern frequently seen in eBL patients. In addition to the influence of malaria in stimulating B-cell expansion, the possibility that mosquito-borne arboviruses are another risk factor for eBL has recently been raised.[3]

Take-home messages

- The key proliferative change to all Burkitt lymphoma cells is the chromosome translocation of MYC to one of the immunoglobulin loci.
- There are many factors that can contribute to stabilising the hyperproliferative, yet apoptotic phenotype that results from MYC overexpression
- There are many roles that Epstein–Barr virus can play in both the formation and maintenance of Burkitt lymphoma.

CONCLUSION

While BL is undoubtedly a disease of *MYC* translocation, there are many other pathological factors which occur around this key event. These factors conspire to increase the probability of translocation or to stabilise the hyperproliferative, yet apoptotic phenotype that results from its overexpression. The patterns with which they occur clearly differ between the immunologically and geographically distinct forms of BL and are frequently indicative of the events leading to their respective pathogenesis. There are many roles that EBV can play in both the formation and maintenance of this disease and current research is actively exploring these mechanisms.

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