Review

Epstein-Barr virus and Burkitt lymphoma

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Abstract

In 1964, a new herpesvirus, Epstein-Barr virus (EBV), was discovered in cultured tumor cells derived from a Burkitt lymphoma (BL) biopsy taken from an African patient. This was a momentous event that reinvigorated research into viruses as a possible cause of human cancers. Subsequent studies demonstrated that EBV was a potent growth-transforming agent for primary B cells, and that all cases of BL carried characteristic chromosomal translocations resulting in constitutive activation of the c-*MYC* oncogene. These results hinted at simple oncogenic mechanisms that would make Burkitt lymphoma paradigmatic for cancers with viral etiology. In reality, the pathogenesis of this tumor is rather complicated with regard to both the contribution of the virus and the involvement of cellular oncogenes. Here, we review the current understanding of the roles of EBV and c-MYC in the pathogenesis of BL and the implications for new therapeutic strategies to treat this lymphoma.

Key words Epstein-Barr virus, Burkitt lymphoma, tumor virus, Malaria, c-MYC

Historical Perspective

Fifty years ago, the idea that viruses might be causative agents of human cancers was controversial. Moreover, all of the then-known viruses in animal models were RNA viruses, raising questions about the discovery by Epstein, Barr, and Achong of a herpesvirus, a DNA virus, in Burkitt lymphoma (BL). Proving that Epstein-Barr virus (EBV) was a driver and not simply a passenger in BL was a difficult task, and it initially relied heavily on epidemiological observations[1,2].

Henle *et al*.[3] provided the first evidence that all African patients with BL were infected with EBV. To do so, they used serological assays they developed to detect the presence of antibodies to EBV capsid antigens. While these assays indicated EBV infection in all African children with BL, the virus was also prevalent in approximately 90% of healthy adults and 30% of children in the United States, where BL was not endemic[3]. Clearly, EBV infection was not, by itself, sufficient to cause BL. It was notable, however, that the incidence of EBV infection in African patients with BL was markedly higher than that in healthy children in the West, suggesting that most African children acquire EBV in the first 2 years of life whereas infection was more likely to be delayed by several years among affluent American populations[4]. The serological responses to EBV were qualitatively and quantitatively different between BL and control groups and during clinical progression, response, and relapse, each in a way that strongly implicated a role for EBV in BL[4-7]. Importantly, African patients with BL not only carried EBV, but the virus was also present in all of the malignant cells in their tumors, as demonstrated by DNA hybridization to detect viral genomes[8] and immunofluorescence to detect the latent infection EBV-encoded nuclear antigen (EBNA)[9,10].

One key piece of evidence complementing the epidemiologic features of BL in Africans was that EBV is able to growth-transform normal resting B lymphocytes into lymphoblastoid cell lines (LCLs) that grow indefinitely in the laboratory[11,12]. EBV clearly has oncogenic potential[13]. The growth-transforming function of EBV is now known to require coexpression of at least 6 latent infection viral genes that encode the nuclear antigens (EBNA1, EBNA2, EBNA3A, EBNA3C, and EBNA-LP) and the latent membrane protein 1 (LMP1)[14,15]. Paradoxically, BL tumors usually express a far more restricted pattern of latent genes (**Figure 1**), with EBNA1 being the only viral protein regularly expressed, along with various non-coding RNA species that are dispensable for transforming function[16-19]. This more restricted pattern of EBV gene expression is insufficient to growth-transform primary B cells, which begs the question, what role does EBV play in the pathogenesis and maintenance of BL?

The high incidence of BL in Africa, ranging from around 3–6 new cases per year per 100,000 children aged 0–14 years[2], was shown by Denis Burkitt to be confined to geographic and climatic areas consistent with involvement of an insect-borne agent[20,21]. This agent was subsequently identified as the *Plasmodium falciparum* malarial

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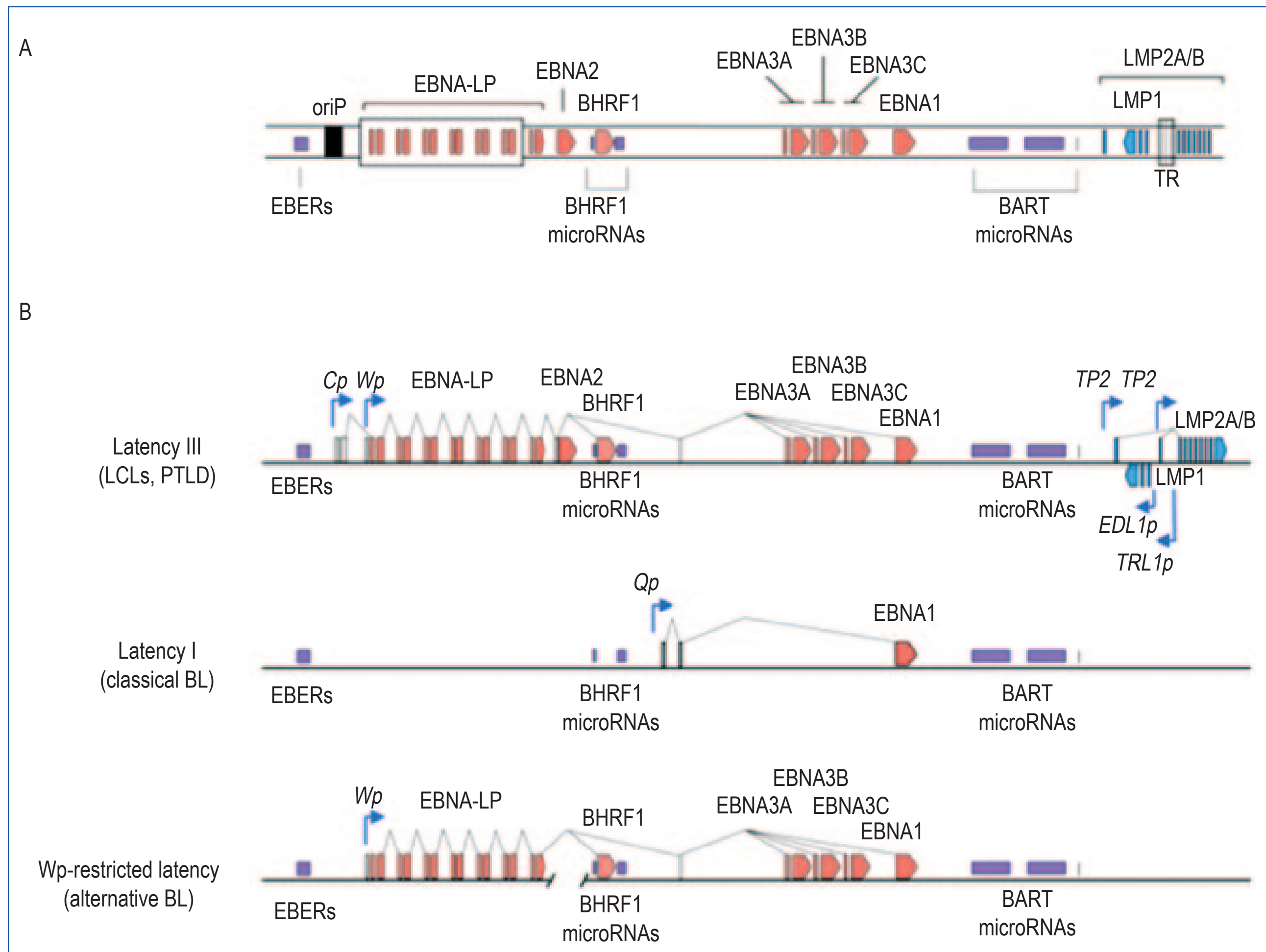

Figure 1. **Epstein-Barr virus (EBV) gene expression in Burkitt lymphoma.** A, organization of the viral genes express during latent, non-productive infection. The schematic is not to scale, and for simplicity the double-stranded DNA episomal viral genome is represented here as a linear genome. The 6 nuclear protein-encoding genes (*EBNAs*; in red) and the latent membrane protein-2A and -2B genes (*LMP2A/B*; in blue) are transcribed in a rightward direction. The latent membrane protein-1 gene (*LMP1*; in blue) is transcribed from the reverse DNA strand. The relative locations of the non-coding RNAs, which include the EBV-encoded non-polyadenylated RNAs (EBERs) and numerous microRNAs, are depicted in purple. The origin of plasmid replication (OriP), which contains dyad repeat and direct repeat elements, is indicated downstream of the *EBER* gene. For reference, the terminal repeat (TR) region is indicated. The TRs are the site of genome linearization during lytic virus replication and re-ligation following latent infection. Because the first coding exon of *LMP2A* (and the first non-coding exon of *LMP2B*) is located to the left of the TR and the common *LMP2A/B*-coding exons are located to the right of the TR, transcription of *LMP2A* from the TP1 promoter and *LMP2B* from the TP2 promoter can only occur from the episomal genome. B, different latent gene transcription patterns. All of the coding and non-coding latent genes are expressed in normal B cells that are directly growth-transformed by EBV. This form of latency (Latency III) is observed in lymphoblastoid cell lines (LCLs) *in vitro* and in post-transplantation lymphoproliferative disease *in vivo*. All 6 *EBNAs* and *BHRF1 vBCL2* are transcribed from the Wp and/or Cp promoters during Latency III. The majority of EBV-positive Burkitt lymphoma tumor biopsies display a Latency I pattern of gene expression in which the non-coding RNAs are expressed, but *EBNA1* is the only protein-encoding gene transcribed. *EBNA1* gene transcription in Latency I is driven from the Qp promoter (in contrast to Latency III in which Cp/Wp-driven transcription occurs). A minority of Burkitt lymphomas carry genomes with a deletion spanning their *EBNA2* gene, from which they display a Wp-restricted form of latency. Wp-driven transcription allows expression of all of the remaining 5 *EBNAs* and also of *BHRF1*, which is expressed at much higher levels than in Latency III LCLs. The absence of *EBNA2* in Wp-restricted latency results in repression of EBNA2-dependent *LMP1* and *LMP2* gene expression.

parasite, which is transmitted by mosquitoes and is holoendemic in the equatorial "tumour belt" mapped by Burkitt[22,23]. Suppression of malaria infection associated with reduced incidence of BL[24], and there is a link between the incidence of BL in Africa and high antibody titers to both EBV and malaria[25,26]. The evidence was, and remains, strongly suggestive that coinfection with EBV and *Plasmodium falciparum* malaria is somehow important in the development of BL[27].

Both EBV and *Plasmodium falciparum* malaria infections are

widespread among children in Africa, yet only a relatively small number of coinfected children develop BL. Clearly other factors are involved. The search for features unique to the tumor revealed characteristic reciprocal chromosomal translocations, always involving chromosome 8 at what is now known to be the c-*MYC* oncogene locus, and most frequently chromosome 14 at the immunoglobulin heavy chain locus or, less commonly, chromosomes 2 or 22 at the immunoglobulin light chain loci[28-30].

While this lymphoma in Africa attracted much attention due to its unusually high incidence and its association with EBV, Gregory O'Conor, who was a colleague of Denis Burkitt in Africa, recognized early on that clinically and histologically indistinguishable lymphomas occurred outside Africa, albeit at much lower and variable incidence, and were not confined to children[31-34]. These so-called sporadic tumors are not associated with malaria and typically show only 10%–20% association with EBV, although this may increase to 30%–60% in BLs arising in human immunodeficiency virus (HIV)-positive individuals[35,36]. Regardless of EBV association and geographic origin, all BLs contain c-*MYC* translocations and a consistent cellular gene expression profile[34,37,38].

EBV and the Pathogenesis of BL

To recap, EBV is known to be widespread in all human communities, and therefore, only a very small minority of infected individuals develop BL or indeed any of the other cancers now linked to the virus. Additionally, not all cases of BL are EBV-associated. By themselves, these facts do not rule out a causative role for EBV in oncogenesis, as cancer arises from multistep genetic events and different genetic events and molecular mechanisms may lead to the same cancer. Consistent with this, the role of EBV in BL pathogenesis is not a simple result of the virus' ability to growth-transform B lymphocytes, as most of the growth-transforming genes necessary for establishing and maintaining LCLs are repressed in BL tumors.

These observations can be reconciled with a role for EBV in BL pathogenesis by supposing that EBV somehow increases the likelihood of generating cellular genetic changes, most importantly *MYC*-activating translocations, which drive lymphoma development. The opportunities for EBV to promote such genetic events are apparent when one considers the mechanisms by which the virus colonizes and persists within the B-lymphocyte compartment of healthy infected people. These events have been extensively reviewed elsewhere[39-42]. While the details are still under debate[42-45], it is broadly agreed that the virus normally enters the B-cell compartment after crossing the epithelial barrier of oropharyngeal lymphoid tissues. Here, infected B cells may express transformation-associated viral genes and proliferate[44,46,47], but the only infected cells that enter the circulating peripheral blood are those with a non-proliferating memory B-cell phenotype and those with repressed expression of transformation-associated viral genes[48,49].

The ability of EBV to induce cell division in lymphoid tissues represents a mechanism for expanding the pool of virus-infected cells, albeit at the cost of rendering the cells susceptible to elimination by virus-specific immune T cells[50]. Conversely, the ability to establish a silent infection in resting memory B cells allows persistence in immune-competent individuals. Thorley-Lawson[41] developed the idea that EBV-transformed, naïve B cells follow the normal B-cell development pathway to generate memory B cells via germinal center reactions, during which EBV gene expression is sequentially repressed. There is some dispute as to whether circulating memory B cells carrying EBV as a silent infection are derived only from infected naïve B cells that subsequently participate in a germinal center reaction, and whether EBV modulates the germinal center reaction or responds to it[42,43,51]. However, it is not disputed that small numbers of EBV-infected cells with more restricted patterns of latent gene expression are found within germinal centers, and in numbers that fit mathematical models of germinal center involvement in EBV persistence[43,45,52].

The significance of EBV-infected cells passing through germinal centers is that these anatomical sites of genetic instability are necessary for B-cell maturation. In germinal center B cells, there is up-regulation of activation-induced cytidine deaminase (AID), which is essential for somatic hypermutation (SHM) and immunoglobulin class-switching, the two genetic events that generate the vast repertoire of B-cell receptors from which clones with highest antigen affinity are selected. EBV-infected naïve B cells participating in germinal center reactions are subject to these genetic events. In addition, as revealed by *in vitro* infection experiments, EBV infection of naïve B cells can induce AID activation and SHM and, with additional T-cell help, immunoglobulin class-switching, raising the possibility that EBV can potentially drive memory B-cell maturation independently of germinal centers[51]. Regardless of whether or not EBV-infected naïve B cells enter the memory B-cell pool via germinal center-dependent or -independent routes, these infected B cells will be subject to genetic trauma *en route* to maturation. The pathogenesis of BL, in common with many other B-cell malignancies, is likely to involve genetic accidents arising from normal processes of B-cell maturation[53], with the most critical, or driver, mutation in the genesis of BL being the c-*MYC* oncogene translocation.

How, then, might EBV contribute to the generation of aberrantly mutated cells? One likely possibility is that its transforming potential allows the survival of aberrantly mutated cells that, in the absence of B-cell receptor (BCR) ligation through high-affinity cognate antigen, would otherwise be scheduled to die by apoptosis. This is evident *in vitro*, where EBV can transform germinal center B cells lacking immunoglobulin expression[54-57], and *in vivo*, where some EBV-positive lymphoproliferations have crippling immunoglobulin gene mutations[58-60]. In this context, expression of the latent membrane protein-2A (*LMP2A*) viral gene might override the need for high-affinity antigen/BCR survival signals, as LMP2A contains an immunoreceptor tyrosine-based activation motif that can replace BCR signals[61-64]. In addition, the EBV-encoded LMP1 protein, which functions similarly to a constitutively active CD40 receptor, can provide prosurvival signals to infected B cells within the germinal center[65-69].

In addition to enhancing the survival of mutated cells, EBV might also be directly involved in promoting genetic instability[70-72]. Various potential mechanisms have been identified, including induction of oxidative stress[71], induction of DNA damage and telomere

dysfunction[70,72,73], activation of recombinases[74], and activation of AID and SHM[51,75].

Malaria, HIV, and the Pathogenesis of BL

The high incidence of BL in Africa is restricted to those geographic areas where *Plasmodium falciparum* malaria is holoendemic. In these areas, EBV is present in tumor cells in virtually all BL cases. By contrast, the association with EBV is less frequent in sporadic BL that occurs worldwide. These observations are consistent with EBV and malaria cooperating to increase the incidence of this lymphoma[36,76]. To a lesser extent, coinfection with HIV also increases both the overall incidence of BL and the frequency of EBV-positive BL[35,36,77-79]. Indeed, Rochford *et al*.[27] have argued that endemic BL is a polymicrobial disease.

Both malaria and HIV induce hypergammaglobulinemia through polyclonal B-cell activation and cause a sustained increase in EBV loads. It was postulated early that the contribution of malaria to BL pathogenesis involves its immunostimulatory effects on B cells[80] and possibly selective activation of the memory B-cell compartment[81,82]. Malaria also impairs T-cell immunity to EBV infection[83-86]. Although this impairment is transient, the substantially increased EBV loads in circulating memory B cells associated with malarial infection are long-lived[87,88]. Malaria's immunostimulatory effects on B cells, which include AID activation, and immunosuppressive effects on T-cell responses, combine to increase both EBV loads and the likelihood of generating and selecting for c-*MYC/IG* gene translocations[27,89].

The Ongoing Contribution of EBV to the Evolved Tumor

Once established, most EBV-associated BL tumors display a Latency I pattern of viral gene expression. Coupled with inherent impairments in antigen processing functions in BL cells, the repressed viral gene expression probably benefits tumors insomuch as they can evade recognition by virus-specific immune T cells[17,90,91]. However, the virus is not simply a subdued passenger at this stage; rather, it continues to contribute to the malignant phenotype. Thus, rare subclones of some BL cell lines that have lost the viral genome display increased sensitivity to apoptosis-inducing agents, reduced growth in low serum or soft agar cultures, and loss of *in vivo* tumorigenicity as xenografts in mouse models[92-94]. The virus appears therefore to provide some survival advantage to malignant cells, even in the absence of most transformation-associated genes.

How EBV effects this enhanced survival advantage is unresolved. Reports on the role of EBNA1[93-96], EBERs[97-99], and the BART microRNAs[100] are sometimes contradictory but generally support the idea that one or more of these viral transcripts contribute to survival in BL cell lines. Most of these studies have been performed on a few select subclones of the Akata-BL cell line, and the generality of the observed protective effects is not clear. Our own recent data on a larger panel of cell lines with EBV loss derived from 5 different parental BL cell lines suggests that the survival advantage of Latency I parental BL lines over derivatives lacking EBV cannot be fully restored by physiological levels of any one of EBNA1, EBERs, or BART microRNAs, but rather requires the cooperative activity of these genes (unpublished data).

Although BL tumors generally display a Latency I form of EBV gene expression, an alternative pattern of viral gene expression was recently identified in a minority of BL cell lines and in their corresponding tumor biopsies[101,102]. Such lines contain EBV genomes with deletions of around 6–8 kb that span the *EBNA2* gene. Here, instead of Q-promoter (Qp)-driven *EBNA1* expression, the W-promoter (Wp) is highly active and drives expression of all *EBNAs* except *EBNA2* (**Figure 1**). Importantly, the broader pattern of latent viral gene expression in these Wp-restricted BLs includes high levels of the *BHRF1* gene encoding a vBCL2 homolog that was previously thought to be exclusively a lytic cycle protein[103]. Interestingly, Wp-restricted BL cell lines usually contain both wild-type genomes and *EBNA2*-deleted genomes, and gene expression seems to be derived entirely from the deleted genomes while the wild-type genomes remain silenced[101]. The mechanism of this selective genome expression is unknown. Because the deleted genomes are derived from wild-type viruses that reside in the same tumor cells, it is possible that such deletions may also arise in other cases of BL that display classical Latency I gene expression. However, the deleted genomes would not be apparent unless the wild-type genomes were silenced and the Wp on the deleted genomes was activated.

Wp-restricted tumors all show characteristic BL morphology, c-*MYC/IG* gene translocations and high c-*MYC* expression. Genome-wide expression arrays of early passage lines and isogenic subclones with different latencies confirmed that Latency I and Wp-restricted BL tumors both fall within the "molecular BL" cellular gene signature, although Wp-restricted tumors were identifiable through up-regulation of certain plasmacytoid differentiation genes[104]. This plasmacytoid shift does not reflect the involvement of a different progenitor cell but, rather, is the phenotype imposed on a common BL progenitor by Wp-restricted latency. Despite expressing many immunogenic latent proteins that are not found in classical Latency I BLs, Wp-restricted BLs are insensitive to $CD8^+$ immune T cells specific for these latent proteins[102]. All BL tumors, whether EBV-negative or EBV-positive, are therefore defective for HLA class I antigen processing, a phenotype that appears to be driven predominantly by overexpression of c-*MYC* and the absence of EBV LMP1[90,105].

Another remarkable consequence of Wp-restricted latency in BL is that it confers a substantial anti-apoptotic phenotype on tumor lines relative to Latency I BL cell lines or EBV-negative BL cell lines[101]. The enhanced resistance to a broad range of apoptotic stimuli is predominantly mediated by Wp-driven expression of the vBCL2 encoded by *BHRF1*[103], aided by contributions from the EBNA3 proteins[106] and miR-BHRF1 miRNAs[107]. The greatly enhanced survival advantage of Wp-restricted BLs raises the question of whether this subset of BL tumors might show different clinical presentation and responses to therapy. This is the subject of ongoing collaborative studies initiated by our group. At present, there is no reliable estimate of the frequency of Wp-restricted tumors. Analysis

of our large panel of Ugandan and Kenyan BL cell lines indicates that approximately 15% of the lines are Wp-restricted, but this is likely an overestimate because not all cultured biopsies generate cell lines and there is likely to be a bias toward successful establishment of vBCL2-expressing lines over Latency I lines. In addition, it is possible that there will be geographical variations in the incidence of Wp-restricted BL due to genetic traits in cellular and/or viral genomes.

The Impact of c-*MYC* Translocation and Other Mutations

The evidence is overwhelming that EBV both increases the incidence of BL and continues to provide a growth and/or survival advantage to the established tumor. What, then, can we say about the majority of sporadic tumors that are EBV-negative? One hypothesis is that EBV is involved in the pathogenesis of most BLs but malignant cells are obliged to either repress most latent viral gene expression or lose the viral genome completely, because of incompatibility between c-*MYC* and *EBNA2*/*LMP1* expression[108] and of immune-selection against EBV transformation–associated proteins[17,90]. Such a "hit-and-run" hypothesis for EBV is hard to prove or disprove, but the available evidence suggests that EBV-negative BLs arise independently of EBV involvement. Most notably, EBV-positive and EBV-negative cases of BL differ in the number of somatic mutations in their immunoglobulin heavy chain (V_H) genes and the involvement of antigen selection, suggesting that virus-associated and virus-independent forms of BL differ in their cells of origin and probably in their pathogenesis[109]. Consistent with this observation, there are also striking differences in the translocation breakpoints in the c-*MYC* locus between EBV-positive and EBV-negative BLs[110-112].

Regardless of the origins of sporadic and endemic BLs, a consistent hallmark of all BLs is translocation and dysregulation of the c-*MYC* oncogene. Indeed, the molecular signature of all types of BL[34,37,38] appears to be largely but not entirely due to expression of c-*MYC*[113]. Furthermore, overexpression of c-*MYC* in human EBV-infected B cells can reproduce some key phenotypic characteristics of BL-derived tumor lines[105,108,114]. However, studies in both humans and murine models of c-*MYC*–induced tumors show that c-*MYC*/*IG* translocations can be detected in normal preneoplastic cells[115-117], inferring that dysregulation of the c-*MYC* oncogene is not by itself sufficient to cause Burkitt lymphoma. Indeed, the evidence now suggests that rather than being an initiator of oncogenic events, c-*MYC* has pleiotropic effects because it acts as a universal amplifier of transcriptionally active genes[118-120]. Therefore, while c-*MYC* can drive cell proliferation through up-regulation of cyclins D and E and down-regulation of the negative regulators, it also enhances normal negative regulation of proliferation, including apoptosis[121] (**Figure 2**).

Animal models of c-*MYC*–induced tumorigenesis have demon-strated synergy between c-MYC and suppression of apoptosis through overexpression of anti-apoptotic *BCL2* family genes[122], inactivation of the pro-apoptotic BH3-only Bcl2 family members, Puma, Noxa, and Bim[123,124], modulation of PI3K signaling[125], or disruption of the ARF/MDM2/p53 pathway[126-128]. There is also evidence that EBNA1 can synergize with c-MYC in lymphomagenesis[129].

Consistent with experimental models showing that inhibition of apoptotic pathways is necessary for c-MYC–induced tumorigenesis, *TP53* mutations are frequently observed in BL[130-134]. The overall incidence of *TP53* mutations is approximately 30%–40% in tumor

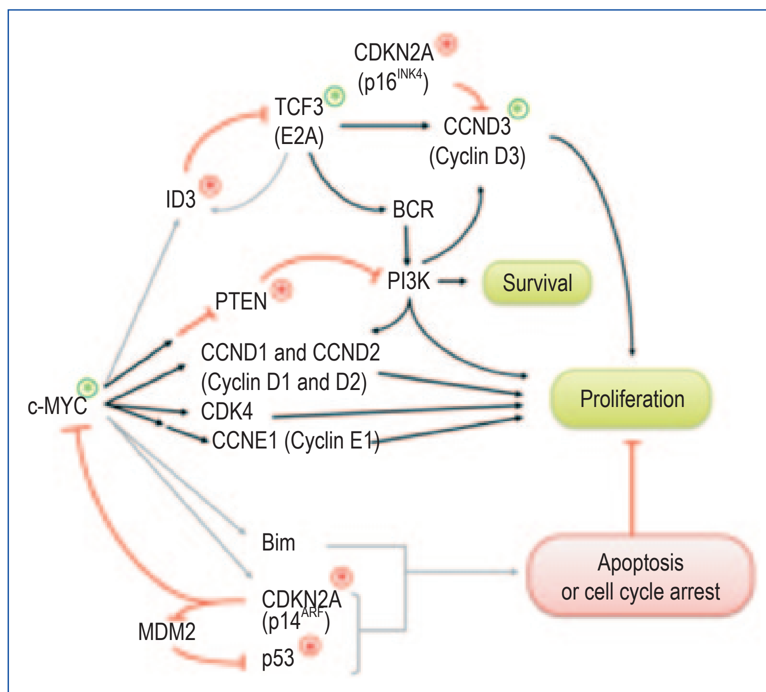

Figure 2. **Cellular gene mutations in Burkitt lymphoma.** Key proliferative and apoptotic pathways induced by c-MYC are indicated in this schematic adapted from Schmitz *et al*.[136] and Kelly & Rickinson[159]. Genes that are frequently mutated in Burkitt lymphoma are indicated. Green asterisks denote gene-activating mutations, while red asterisks denote inhibitory mutations.

biopsies and approximately 60%–70% in established BL cell lines, regardless of the EBV status of the tumors. Other genetic and epigenetic alterations involved in complementing c-MYC activation in BL have been identified in the p14ARF/MDM2/p53 pathway [135].

A shift from targeted gene analysis to global genetic analysis, made possible by a new generation of sequencing technologies, has transformed our understanding of the genetic landscape of BL. Independent studies by Schmitz *et al*.[136], Richter *et al*.[137], and Love *et al*.[138] have integrated structural and functional genomics to catalog the broad range of somatic mutations in BL. The most commonly mutated gene was c-*MYC* itself, which was mutated in approximately 70% of BL[136-138]. This observation was consistent with a previous study that showed c-*MYC* to be hypermutated in BL, possibly due to translocation-induced juxtaposition with the immunoglobulin gene[139]. Activating mutations in c-*MYC* can dramatically alter target gene responses to increase c-*MYC*'s oncogenic potential in BL[140], again highlighting the fact that the c-*MYC*/*IG* translocation alone is insufficient to drive lymphomagenesis.

A surprising observation from the game-changing structural and functional genomic studies was the frequent involvement of *ID3*, *TCF3* (encoding E2A), and *CCND3* (encoding cyclin D3) mutations, implicating a new pathway of oncogenic cooperation in the pathogenesis of BL. A summary of how some of the more common mutations in BL tumors affect the proliferative and apoptotic functions of c-MYC is shown schematically in **Figure 2**. The *ID3* gene, a direct transcriptional target of c-MYC[141], is a negative regulator of *TCF3*. In BL, inactivating mutations of *ID3* and activating mutations of *TCF3* result in enhanced E2A function, which activates proliferation through induced cyclin D3 expression and survival through activation of PI3K signaling[136]. Interestingly, the mutations in *ID3* and/or *TCF3* were more common in sporadic BL (70%) than in endemic BL (40%), providing the first convincing evidence that the pathogenesis of EBV-negative BL requires more oncogenic mutations than EBV-positive BL.

New Therapeutic Targets

While Burkitt[142] initially found BL in African children to be exquisitely sensitive to chemotherapy, relapses of this aggressive lymphoma do occur and the initial promise of curative therapy faded. Certainly, the prospects for sporadic adult BLs were poor. The development of multi-agent chemotherapy and immunotherapy has led to marked improvements, although toxicities remain significant[143-149].

The scope for new targeted therapies has been widened by recent advances in identifying new pathways essential for the pathogenesis of BL, most notably the ID3/E2A/cyclinD3 pathway[136-138]. In addition, the recent detailed genetic mapping of BL also confirmed the importance of previously recognized targets that are ripe for exploitation. These include inhibitors of c-MYC[150-152], PI3 kinase[153-155], and BCL2 family members[156,157]. Finally, while the effectiveness of EBV-targeted immunotherapy for virus-associated cases of EBV may be diminished by the inherent impaired antigen presentation functions of malignant cells[90,102], small-molecule inhibitors of EBNA1 function represent a promising strategy in combination with other treatments[158].

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