Review

Epstein-Barr Virus and Cancer

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Abstract

EBV was the first human virus to be directly implicated in carcinogenesis. It infects >90% of the world's population. Although most humans coexist with the virus without serious sequelae, a small proportion will develop tumors. Normal host populations can have vastly different susceptibility to EBV-related tumors as demonstrated by geographical and immunological variations in the prevalence of these cancers. EBV has been implicated in the pathogenesis of Burkitt's lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, nasopharyngeal carcinoma, and lymphomas, as well as leiomyosarcomas arising in immunocompromised individuals. The presence of this virus has also been associated with epithelial malignancies arising in the gastric region and the breast, although some of this work remains in dispute. EBV uses its viral proteins, the actions of which mimic several growth factors, transcription factors, and antiapoptotic factors, to usurp control of the cellular pathways that regulate diverse homeostatic cellular functions. Recent advances in antiviral therapeutics, application of monoclonal antibodies, and generation of EBV-specific CTLs are beginning to show promise in the treatment of EBV-related disorders.

Introduction

EBV is a member of the herpesvirus family. As with other herpesviruses, EBV is an enveloped virus that contains a DNA core surrounded by an icosahedral nucleocapsid and a tegument. Family members include herpes simplex I and II and varicella-zoster virus (alphavirus subfamily), cytomegalovirus and human herpesvirus 6 and 7 (betaherpesvirus subfamily), and human herpesvirus 8 and EBV (gammaherpesvirus subfamily; Ref. 1). Human tumors have been attributed to both human herpesvirus 8 (Kaposi's sarcoma, primary effusion lymphoma, and Castleman's disease) and to EBV (Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkin's and non-Hodgkin's lymphomas). Although herpesviruses are ubiquitous in nature, humans serve as the only natural host for EBV.

It is now known that EBV infects >90% of the world's adult population. Upon infection, the individual remains a lifelong carrier of the virus (2). EBV is transmitted by salivary contact. During acute infection, EBV primarily infects and replicates in the stratified squamous epithelium of the oropharynx (3, 4). This is followed by a latent infection of the B lymphocytes (although the sequence of epithelial *versus* lymphoid infection is a matter of debate). EBV infection of B lymphocytes is thought to occur in the oropharyngeal lymphoid organs, and in normal carriers, the virus persists in circulating memory B cells (5–7). The B-lymphotropic nature of EBV is evidenced by the ability of the virus to immortalize normal resting B lymphocytes *in vitro*, converting them into permanently growing lymphoblastoid cell lines (8). Virus shedding into saliva occurs most consistently during primary infection, but virus can continue to be shed from the oropharynx into the saliva for years (3, 7). Of interest, once the virus has colonized the B-lymphoid compartment, reactivation from latency can occur at any mucosal site where B cells reside (*e.g.*, the cervix).

Primary infection with EBV typically occurs within the first few years of life and is generally asymptomatic in most underdeveloped countries. In more developed areas, primary infection can be delayed until late adolescence or adulthood and results in infectious mononucleosis in some cases (9). Long-term EBV coexists with most human hosts without overt serious consequences. However, in some individuals, the virus is implicated in the development of malignancy.

Historical Perspective

In 1958, Denis Burkitt (10) described a common cancer primarily affecting children in specific regions of Africa. Burkitt believed a virus might be responsible for the cancer, given the climatic and geographic distribution of the cases. EBV was first identified in 1964 when Anthony Epstein's group discerned virus-like particles by electron microscopy in a cell line that had been established from a Burkitt's lymphoma biopsy (11). Later, it was found that sera from patients with the lymphoma that Burkitt had described had much higher antibody titers to EBV than did controls without the lymphoma. The subsequent detection of EBV DNA in Burkitt's lymphoma and the experimental production of lymphomas in cotton-top marmosets and owl monkeys established EBV as the first virus clearly implicated in the development of a human tumor (11).

Molecular Biology of EBV

EBV is a herpesvirus with a 184-kbp long, double-stranded DNA genome that encodes >85 genes (12). The viral genome consists of a series of 0.5-kb terminal direct repeats at either end and internal repeat sequences that serve to divide the genome into short and long unique sequence domains that have most of the coding capacity (13). EBV, as with other herpesviruses, has a toroid-shaped protein core wrapped with double-stranded DNA, a nucleocapsid with 162 capsomeres, a protein tegument between the nucleocapsid and envelope, and an outer envelope with external glycoprotein spikes (14).

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When EBV infects a cell, the DNA becomes a circular episome with a characteristic number of terminal repeats, depending on the number of terminal repeats in the parental genome, with variation introduced during viral replication. If the infection is permissive for latent infection but not replication, future generations will have EBV episomes with the same number of terminal repeats [therefore, whether the number of terminal repeats have been conserved in a group of latently infected cells can be useful in eludicating if these cells arose from a single cancer-infected progenitor or from multiple progenitors (12–15)].

Two subtypes of EBV are known to infect humans: EBV-1 and EBV-2. EBV-1 and EBV-2 differ in the organization of the genes that code for the EBV nuclear antigen (EBNA-2, EBNA-3a, EBNA-3b, and EBNA-3c; Ref. 16). EBV-2 transforms B cells less efficiently than EBV-1 *in vitro*, and the viability of EBV-2 lymphoblastoid cell lines is less than that of EBV-1 lines (17). The differences in transforming efficiency of the EBV subtypes may relate to divergence in the EBNA-2 sequences (18, 19).

Epidemiology of EBV Infection

As mentioned earlier, the vast majority of the world's population exhibits antibodies to EBV and the infection usually occurs early in childhood (2). EBV-1 and EBV-2 differ in geographic distributions. EBV-1 is observed more frequently in most populations. However, EBV-2 is nearly as prevalent as EBV-1 in New Guinea, as well as in equatorial Africa (20, 21). Endemic Burkitt's lymphoma and holoendemic malaria are common in equatorial Africa, and it has been shown that almost half of all African Burkitt's lymphoma tumors carry EBV-2. In contrast, 85% of nasopharyngeal carcinomas in Taiwan contain EBV-1 (22). Immunocompromised patients also more commonly harbor both subtypes of EBV (23). Taken together with the attenuated transforming ability of EBV-2, these data suggest that it may be necessary for a preexisting immunosuppressed condition (HIV or malaria) to exist for EBV-2 to be capable of maintaining a B-lymphocytic infection and causing transformation (17). On the other hand, studies showing that HIV-infected hemophiliacs have lower rates of EBV-2 infection than HIV-infected homosexuals have challenged the notion that EBV-2 superinfection relates to immunodeficiency; rather, the latter observation ascribes the acquisition of EBV-1 *versus* EBV-2 entirely to exposure (24).

EBV Infection

EBV is transmitted from host to host via saliva. Primary infection begins at the oropharyngeal epithelium. B lymphocytes are infected as they traffic in close proximity to these cells. (This sequence of events is, however, still controversial.) In normal individuals, the result is clinically apparent or milder forms of infectious mononucleosis. In acutely infected B lymphocytes, EBV expresses proteins causing cell proliferation. An EBV-specific CTL response occurs in healthy people and probably accounts for the fall in infected B cells from levels as high as 10% in acute EBV infection to 1 in 10^6 cells with convalescence (Fig. 1).

In a primary EBV infection, three antibodies (-IgG, -IgM, and -IgA) are produced against EBV viral capsid antigen, two antibodies (-IgG and -IgA) are produced in response to early antigen D, and one antibody (-IgG) is produced in response to early antigen R (25). During a latent infection, EBNA-3A, EBNA-3B, and EBNA-3C all elicit specific CTL responses, which seem to be the dominant latency response to EBV proteins (26–28).

EBV infection of B cells begins with the attachment of the gp 350/220 viral membrane glycoprotein to the CD21 molecule on these lymphocytes (29). Postattachment events are complex. CD21 becomes cross-linked, which triggers an initial activating signal that is thought to prepare the cell for EBV infection. EBV binding to CD21 immediately activates tyrosine kinase *lck* and mobilizes calcium (30, 31). This is followed by an increase in mRNA synthesis, blast transformation, homotypic cell adhesion, surface CD23 expression (a characteristic surface marker for activated B cells), and interleukin (IL)-6 production (32–34). The viral genome is then uncoated and delivered to the nucleus where it immediately circularizes. Circularization and W promoter expression launch an ordered cascade of events that leads to the expression of all of the EBNA proteins and the two latent membrane proteins (LMPs; Ref. 35). The EBV nuclear antigen leader protein (EBNA-LP) and EBNA-2 proteins are the first proteins to be detected upon EBV infection (36, 37). At 24–48 h after infection, a promoter shift occurs where the C promoter (Cp) is used in favor of the initial promoter W promoter (reviewed in Ref. 38). Initially, it was hypothesized that the switch from the Wp to Cp promoter coincided with the switch to an expanded pattern of splicing that allows expression of EBNA-3A, EBNA-3B, EBNA-3C, and EBNA-1 (39–41). It is now known that the expanded pattern of splicing likely precedes the promoter switch (42). This is consistent with the data that suggests that the downstream EBNAs regulate promoter Cp activation (43–48). All of the EBNA transcriptional products are involved in transcriptional control and participate in the activation of the expression of the viral LMP-encoding genes (LMP-1 and LMP-2) and several cellular genes. The combined action of these viral and cellular proteins serves to initiate cellular S-phase 24–48 h after infection (38).

After the initial infection, EBV persists in a circulating subset of resting memory B cells in healthy individuals at a frequency of $\sim$1 in 1×10^5 to 1×10^6 cells. The viral genome is generally episomal and present in low numbers in the host cell's nucleus. Immunosuppressive states permit spontaneous replication of the episomal virus in circulating B cells, as observed in acute infectious mononucleosis. Immunocompetent carriers control latent EBV infection via CTLs. Loss of the EBV-specific CTL may permit the development of lymphoma.

Besides, its well-known tropism for B cells, the targets of EBV infection may also include epithelial cells, T cells, and cells of the macrocytic, granulocytic, and natural killer lineages. These cells may be infected by mechanisms different from the CD21-mediated internalization typical in B cells.

EBV Products

EBV encodes a series of intriguing products (Table 1). These products interact with or exhibit homology to a wide variety of antiapoptotic molecules, cytokines, and signal trans-

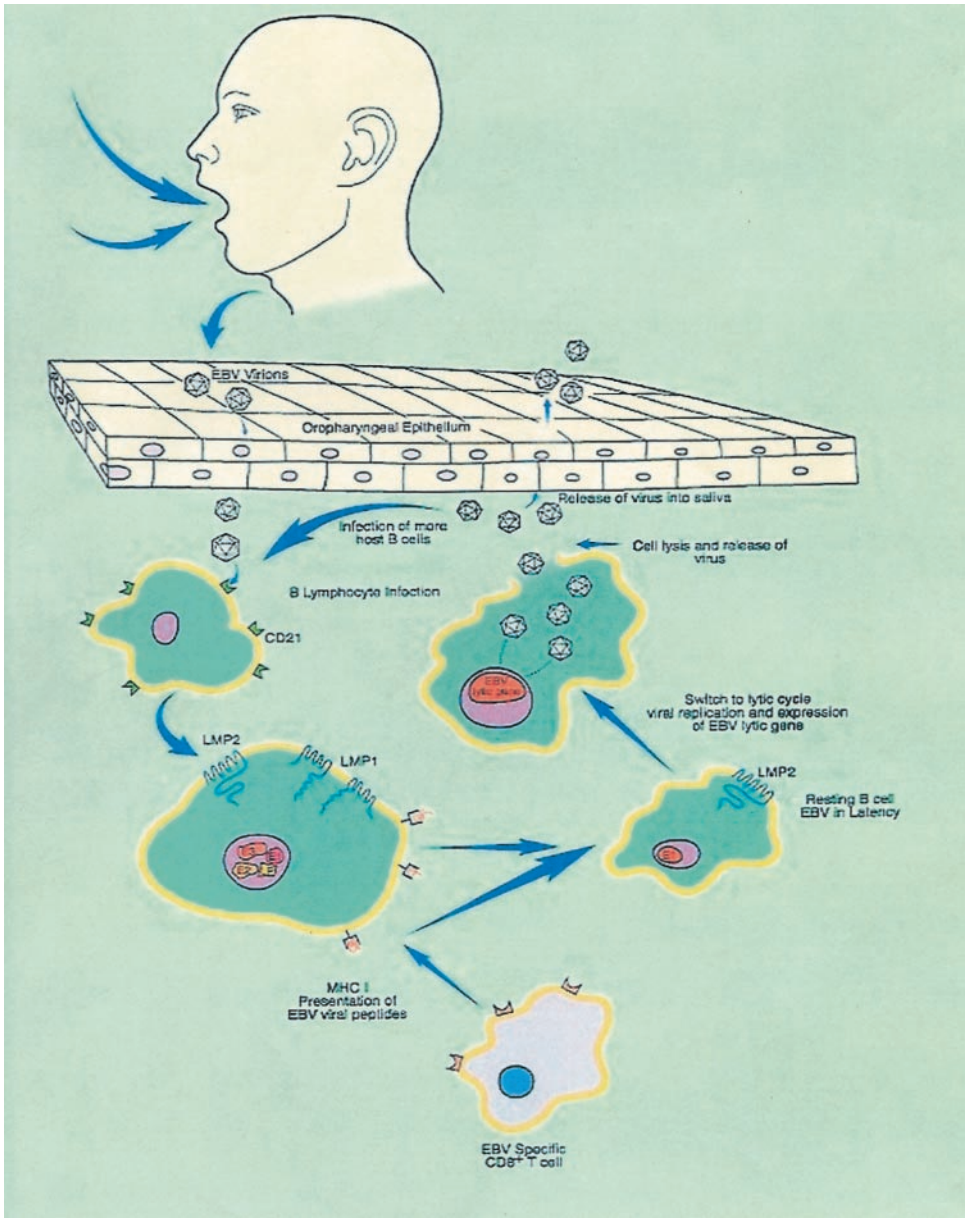

Fig. 1 The EBV life cycle. Infection is transmitted from host to host via saliva, and the virus passes through the oropharyngeal epithelium to the B lymphocytes. The virus enters the B cell and causes it to proliferate and spread through the B-cell compartment. T cells respond and control B-cell proliferation. Resting EBV-infected B cells with limited antigen presentation persist at a frequency of 1 in 1×10^5-10^6 cells and constitute the long-term viral reservoir. Intermittently, these resting B cells will enter the lytic cycle and lyse, releasing virions back into the saliva while also infecting more host B lymphocytes.

ducers, hence promoting EBV infection, immortalization, and transformation.

EBNA-1. EBNA-1 is a sequence-specific DNA binding phosphoprotein that is required for the replication and maintenance of the EBV genome (49). It also has a central role in maintaining latent EBV infection.

The EBNA-1 coding sequence lies in the BKRF1 open reading frame (50–53). EBNA-1 binds to the origin of plasmid replication, which is composed of two distinct EBNA-1 binding elements (54–59). These are the family of repeats and the dyad symmetry (60). The family of repeats and the dyad symmetry binding elements both contain multiple 18-bp EBNA-1 binding sites (60). The family of repeats element contains 20 binding sites, whereas the dyad symmetry element only contains 4 EBNA-1 binding sites (61). Upon binding of EBNA-1 to the plasmid origin of replication, EBV uses host enzymes to mediate all remaining steps in replication. EBV genome replication also only propagates rightward because the family of repeats element aborts leftward replication causing episomal replication to begin and end at the plasmid origin of replication (62, 63). EBNA-1 binding sites are also located at +10 and +34 nucleotides downstream of promoter Qp (64). It is thought that promoter Qp operates in response to many transcription factors to ensure and maintain EBNA1 levels but is subject to feedback regulation by excess EBNA-1 (65).

EBNA-2. EBNA-2 is a transcriptional coactivator that coordinates viral gene expression in latency III and also transactivates many cell genes while playing a critical role in cell

Table 1 Overview of EBV products and functions[a]

Protein	Function
EBNA1	Essential for EBV immortalization of cell, replicates EBV genome, segregates viral episomes at mitosis.
EBNA2	Transcriptional coactivator that upregulates expression of viral and cellular genes (especially *c-myc*), essential for EBV immortalization of cell, one of first viral proteins produced during EBV infection.
EBNA3	
3A	Essential for EBV immortalization of cell, interacts with CBF1.
3B	Not essential for EBV immortalization of cell, interacts with CBF1, function remains largely unknown.
3C	Essential for EBV immortalization of cell, overcomes retinoblastoma protein (pRB) checkpoint in cell cycle, interacts with CBF1, increases production of LMP1.
EBNA-LP	Interacts with EBNA2 to inactivate *p53* and *Rb*, interacts with transcription factors in notch signaling pathway, one of first viral proteins produced during EBV infection, redistributes EBNA3A in nucleus, contributes to EBV immortalization of cell.
LMP1	Mimics CD40 ligand binding signal, elevates levels of *bcl-2* and *a20*, acts a constitutively active receptor, essential for EBV immortalization of cell.
LMP2A and B	Drives EBV into latency. May play a role in oncogenesis in Hodgkin's disease and nasopharyngeal carcinomas.
EBER1 and 2	Forms complexes with L22, associates with PKR, not essential for EBV immortalization of cell.
CSTs or BARTs	Complementary strand transcripts encoded at high levels in nasopharyngeal carcinomas. Potential protein products may modify *Notch* signaling.

[a] Summarized from references 15, 38, 43, 44, 49–114.

immortalization (53, 54, 66). EBNA-2 (and EBNA-LP) are the first latent proteins detected after EBV infection (3). There are two distinct types of EBNA2 that are identified serologically. These two serological types correspond to EBV-1 and EBV-2 (35, 67, 68).

EBNA2 primarily serves to up-regulate the expression of viral and cellular genes. Among these are CD23 (a surface marker of activated B-cells), *c-myc* (a cellular proto-oncogene), and viral EBNA-C promoter (44, 69, 70). This up-regulation is achieved not by binding DNA directly but by binding other transcription factors (most notably, the viral Cp binding factor 1), consequently bringing the strong transcription domain of EBNA-2 close to the C promoter (53, 66, 71). However, the transcriptional activation effects of EBNA-2 are not limited to interaction with Cp binding factor 1. There is now evidence that a second Cp binding factor increases the ability of low levels of EBNA-2 to transactivate Cp (43). EBNA-2 is also known to interact with other transcription factors involved in the *Notch* signaling pathway (71, 72). This pathway is important in cell fate determination in the fruit fly and may play a role in development of T-cell lymphoma in humans. It is likely that many other factors are yet to be discovered that interact with EBNA-2 and aid in transactivating both cellular and viral gene expression.

EBNA-LP. EBNA-LP, also known as EBNA-5, is one of the first viral proteins produced during EBV infection of B cells (53). EBNA-LP interacts with EBNA-2 to drive resting B lymphocytes into the G_1 phase of the cell cycle (73) by binding and inactivating cellular *p53* and *retinoblastoma* protein tumor suppressor gene products (74). This is evidenced by the induction of the cyclin D2 RNA in uninfected primary B cells (73) and in the induction of the promoter for LMP-1 in some type I Burkitt's lymphoma cell lines (75). It has also been shown that EBNA-LP interacts with other transcription factors involved in the *Notch* signaling pathway (71, 73). However, more remains to be understood on the function of EBNA-LP in transformation and during the viral life cycle.

The EBNA-LP gene is characterized by a great deal of RNA splicing. The EBNA-LP open reading frame is derived from repeating W1 and W2 exons of the major internal repeat unit and the unique YI and Y2 exons just downstream of the internal repeat unit. During the assembly of leader exons from primary transcripts, a phenomenon known as exon skipping occurs. Any number of exons in the internal repeat unit or Y1 and Y2 may be skipped during assembly. However, there is one rule for this exon skipping: W1 and W2 appear to be always skipped in pairs. At the 3′ end of the leader exon, virtually any exon may be spliced, creating a huge variety in the potential ends for EBNA-LP (reviewed in Ref. 38). It is known that the Y1 and Y2 genes are very important in the immortalization process. EBVs with deletions or point mutations preventing the expression of Y1 and Y2 have a decrease in immortalization efficiency of at least 10-fold (76, 77).

EBNA-3A, EBNA-3B, and EBNA-3C. EBNA-3A, EBNA-3B, and EBNA-3C are transcriptional regulators (3). EBNA-3A and EBNA-3C are crucial for *in vitro* B-cell transformation, whereas EBNA-3B is dispensible (3).

EBNA-3 family members are encoded by three genes that are adjacent on the viral genome (53). Conserved sequences are confined to the NH_2-terminal third of the molecules (38). Divergence in EBNA-3A, EBNA-3B, and EBNA-3C between the two subtypes of EBV (EBV-1 and EBV-2) is apparent, given that the primary sequences of these genes are only 84, 80, and 72% homologous, respectively (78).

EBNA-3A and EBNA-3C have been shown to both be essential in immortalization (79, 80). EBNA-3C may overcome the retinoblastoma (*retinoblastoma* tumor suppressor gene checkpoint in the G_1 phase of the cell cycle (81). EBNA-3C has also been shown to increase the production of LMP-1 in some conditions (82). LMP-1 facilitates transformation and cell growth and inhibits apoptosis (see discussion below).

All three EBNA-3s interact with Cp binding factor 1. Cp binding factor 1 is involved in the notch signaling pathway and overexpression of the notch protein has been observed in human T-cell malignancies (83, 84). How each individual EBNA3 proteins regulate Cp binding factor 1-mediated gene expression

is not clear. Recently, EBNA-LP has been shown to cause a redistribution of EBNA3A within the nucleus (44). This tends to point to a model where EBNA-3 proteins participate in a network consisting of all of the EBNA transcription factors, each affecting the other's behavior (38).

LMP-1. LMP-1 is involved in transformation by acting as a constitutively active receptor (CD40) and hence mimics the cellular growth signal that normally results from the binding of CD40 ligand (85, 86). LMP-1 has been most directly linked to oncogenesis by virtue of its ability to recruit an array of cellular genes. It also inhibits apoptosis by elevating levels of Bcl-2 (85).

LMP-1 is an integral membrane protein with six hydrophobic membrane-spanning segments and a COOH-terminal cytoplasmic tail, which contains the effector (87). LMP-1 aggregates in patches on the plasma membrane that are similar to patches formed by ligand-engaged growth factor receptors (88). Mutational analyses have demonstrated that the NH_2 terminus and the transmembrane segments of LMP-1 are responsible for membrane aggregation and that this aggregation is essential for immortalization (89).

LMP-1 mimics CD40 by associating with the same tumor necrosis factor receptor-associated factors (TRAFs; Refs. 85, 90). The COOH-terminal domain of LMP-1 interacts TRAF-1 and TRAF-2 and with tumor necrosis factor receptor-associated death domain protein (91–95). TRAFs and tumor necrosis factor receptor-associated death domain interaction are mediated by separate regions of the LMP-1 COOH-terminal domain, known as transformation effector sites (92, 93). Transformation effector site-1 binds TRAFs, and transformation effector site-2 binds tumor necrosis factor receptor-associated death domain. At least four signaling pathways, namely nuclear factor-κB, c-Jun NH_2-terminal kinase, p38 mitogen-activated protein kinase, and Janus kinase/signal transducers and activators of transcription are implicated in the function of LMP-1 (96–99). These molecules affect diverse signaling cascades. Nuclear factor-κB is a key transcription factor involved in regulation of cell growth and apoptosis. It also controls expression of numerous cytokines, including ones such as lymphotoxin, which is an autocrine growth factor for EBV-transformed cells (92). p38/mitogen-activated protein kinase is also a central signaling pathway and activates the ATF2 transcription factor. Meanwhile, the Janus kinase/signal transducers and activators of transcription cascade integrates with the activator protein-1 transcription factor pathway.

The activating cascades associated with LMP-1 lead to the enhanced expression of B-cell adhesion molecules (LFA1, CD54, and CD58), enhanced expression of B-cell activation markers (CD23, CD39, CD40, CD44, and HLA class II), and morphological changes such as cellular clumping (85, 93, 101–103). The LMP-1 interactions also cause an overexpression of proteins BCL-2 and A20, which protects the infected cell from p53-mediated apoptosis (104, 105).

LMP-2A and LMP-2B. The LMP-2 gene encodes two proteins: LMP-2A and LMP-2B. These proteins are both integral membrane proteins that differ in their NH_2-terminal domains. LMP-2A carries an extra 118-residue domain encoded in exon 1, whereas the LMP-2B exon 1 is noncoding (reviewed in Ref. 38). The NH_2-terminal domain of LMP-2A is cytoplasmic and contains an immunoreceptor tyrosine-based activation motif (106).

A synthesis of the data supports a role for LMP-2 in modifying normal B-cell development to favor maintenance of EBV latency in the bone marrow (3). The expression of LMP-2A in Hodgkin's disease and nasopharyngeal carcinoma suggests an important, as yet unknown, function for this protein in oncogenesis (3).

EBV-Encoded RNAs 1 and 2 (EBERs 1 and 2). EBERs 1 and 2 are nonpolyadenylated, uncapped, noncoding RNAs of 167 and 172 nucleotides, respectively (Ref. 15, reviewed in Ref. 38). They are expressed abundantly in nearly all EBV-infected cells with the exception of oral hairy leukoplakia lesions from AIDS patients and some hepatocellular carcinomas (110). EBERs 1 and 2 (in addition to the two LMPs) are expressed in all forms of latency (3). EBERs have been implicated in the induction of autocrine growth factors and in maintaining the malignant phenotype of Burkitt's lymphoma cells, all of which supports a potential role for these RNAs in oncogenesis (reviewed in Ref. 114).

EBER1 has been shown to form complexes with and relocalize the cellular ribosomal protein L22, (111, 112). EBERs also associate with the IFN-inducible dsRNA-dependent protein kinase (114). IFN-inducible dsRNA-dependent protein kinase is known to mediate protein synthesis control by dsRNA and has also been reported to phosphorylate the inhibitory subunit inhibitor of nuclear factor-κB of the nuclear factor-κB transcription factor. In addition, transfection of the EBER genes into the EBV-negative Akata cell line restored the oncogenic potential that was originally present in the EBV-positive Akata cells but was lost in the EBV-negative subclones (113). Even so, recombinant EBV with EBER genes deleted can transform lymphocytes, suggesting that EBERs are nonessential for transformation (109). In essence, therefore, the role of EBER in transformation is still an open question.

Complementary Strand Transcripts or Bam A Rightward Transcripts. Complementary strand transcripts (or Bam A rightward transcripts) are transcribed from a region mapping to the Bam H1A fragment of the viral genome (112). These transcripts are present in many types of EBV infections but are especially high in nasopharyngeal cancers. They are expressed at lower levels in the other types of latency. Differential splicing of Bam A rightward transcripts yields a family of transcripts, which encompass an open reading frame BARF-O. Potential proteins products are still subject to debate.

Human Protein Homologues

EBV encodes several important proteins that show sequence and functional homology to diverse human proteins (Ref. 115; Table 2).

BCRF1 and IL-10. EBV BCRF1 protein shows 84% sequence homology to human IL-10 (116). IL-10 was first recognized for its ability to inhibit activation and effector function of T cells, monocytes, and macrophages. IL-10 is also a known growth and activation factor for B cells (117, 118). EBV-derived IL-10 is thought to play a role in the establishment of latent infection by suppression of the host immune system (119–121).

Table 2 Homology of EBV genes[a,b]

Viral gene	Human homologue	Functional homology
BCRF1	Interleukin 10	Yes
BDLF2	Cyclin B1	Unknown
BHRF1	BCL-2	Yes
BARF1	C-FMS receptor	Yes
	ICAM-1 (CD54)	Unknown

[a] Summarized from Refs. 115–126.
[b] Amino acid homology between viral and human product varies from ~20% to >80%.

BDLF2 and Cyclin B1. On the basis of sequence alignment, homology between the BDLF2 protein and human cyclin B1 has been suggested (115). Human cyclin B1 regulates the G_2-M transition in the cell division cycle by activating particular cyclin-dependent protein kinases. Very little is known about BDLF2. It has been detected in oral hairy leukoplakia but not in other diseases characterized by latent infections. It has been suggested that it is a late gene expressed during the lytic cycle (115).

BHRF1 and BCL-2. BHRF1 shows partial (25%) sequence homology to the human BCL-2 proto-oncogene, and both have been shown to protect human B lymphocytes from apoptosis (122). BHRF2 products can also interfere with epithelial cellular differentiation (123). BHRF1 may enhance cell survival, allowing oncogenic mutations to accumulate; it may also permit the production of a maximum number of virions through the inhibition of apoptosis (124).

BARF-1 and Intracellular Adhesion Molecule 1. BARF-1 produces a protein that shows some homology to the intracellular adhesion molecule 1, as well as the human colony-stimulating factor 1 receptor (125, 126). Evidence supports BARF-1 being involved in immune suppression by either being an antagonist to colony-stimulating factor 1 receptor or by occupying intracellular adhesion molecule 1 receptors on T lymphocytes without leading to the proper stimuli necessary for T-cell activation (126, 127).

Patterns of EBV Gene Expression

All EBV-associated cancers involve the virus's latent cycle. Four types of latent gene expression have been described. In healthy individuals, the virus persists episomally in resting memory B cells. Of the ~100 viral proteins, only LMP-2 is expressed. In addition, the small polyadenylated viral RNAs designated as EBERs 1 and 2 are also discerned. This type of latency has been designated type 0.

The other three types of latency characterize a heterogenous group of malignancies. Latency I, II, and III are based on patterns of expression of the EBV genome (Table 3). All three types of latency express BARF-0s. During latency I, EBNA-1 and the EBERs are expressed (127). Latency I is generally associated with the EBV-related malignancy Burkitt's lymphoma (127). Latency II has been associated with Hodgkin's disease, T-cell non-Hodgkin's lymphoma, and nasopharyngeal carcinoma (129). EBV gene expression in latency II is usually limited to EBNA-1, the EBERs, LMP-1, and LMP-2A and LMP-2B (130). The final pattern of gene expression (latency III) occurs mainly in immunocompromised individuals suffering from posttransplant lymphoproliferative disorders, AIDS-related proliferative disorders, and in lymphoblastoid cell lines (131). Latency III usually involves the unrestricted expression of all EBNAs, EBERs, and LMPs (130). EBV gene products induce an immune response; however, the immunocompromised state of the host allows for unrestricted gene expression without the consequences such expression would normally elicit in an immunocompetent host.

Oncogenic Features of EBV

To be oncogenic, EBV must maintain its viral genome in the cell, avoid killing the cell, and prevent the cell from becoming a target for destruction by the immune system. Finally, the virus must activate cellular growth control pathways. To maintain viral DNA in the cell, EBV establishes latent infection in B lymphocytes. The EBV genome is maintained in these cells, either as a multicopy circular episome in the host cell or by integrating the viral DNA into the host genome. The virus thus ensures transmission to cell progeny when B lymphocytes replicate. EBV latent genes induce an activated phenotype in the infected B cells. Although these cells are not transformed, if they proceed unchecked or acquire oncogenic mutations, they can become neoplastic. In normal individuals, cytotoxic T-cell responses against latent viral proteins prevent the expansion of

Table 3 EBV latency pattern and associated malignancies[a]

Latency type	Viral genes expressed	Associated malignancies	Refs.
Latency I	EBNA-1 EBERs BARF0	Burkitt's lymphoma	127, 128
Latency II	EBNA-1 EBERs LMP-1 LMP-2 BARF0	Hodgkin's disease Nasopharyngeal carcinoma Peripheral T/NK lymphoma	130, 130
Latency III	All EBNAs EBERs LMP-1 LMP-2 BARF0	AIDS-associated lymphomas Posttransplant lymphoproliferative disorders	130, 131

[a] Summarized from Refs. 127–131.

Table 4 Characterization of EBV-associated malignancies[a]

Malignancy	Subtype	EBV gene expression pattern	% EBV positivity
Burkitt's lymphoma	Endemic	Latency I	>95%
	Nonendemic		15–30%
Hodgkin's disease	MC	Latency II	70%
	LD		>95%
	NS		10–40%
	LP		<5%
Non-Hodgkin's lymphoma	Nasal T/NK	Latency II	>90%
	Angioimmunoblastic Lymphadenopathy	Latency II	Unknown
Nasopharyngeal carcinoma	Anaplastic	Latency II	>95%
Breast Cancer	Medullary carcinoma Adenocarcinoma	Not clear	0–51%
Gastric Cancer	Lymphoepithelioma-like	Controversial novel LMP-1 negative	>90%
	Adenocarcinoma	Latency III	5–25%
Posttransplant lymphoproliferative disorders		Latency III	>90%
AIDS-associated lymphomas	IP-CNS	Latency III	>95%
	Other		30–50%
Leiomyosarcomas in immunosuppressed individuals	Leiomyosarcomas varies	Unclear	Frequent

[a] Summarized from Refs. 15, 24, 53, 125, 129, 132–283.
[b] MC, mixed cellularity; IP-CNS, immunoblastic primary central nervous system lymphoma; LD, lymphocyte depleted; LP, lymphocyte predominant; NK, natural killer; NS, nodular sclerosing.

these activated B cells. Through normal differentiation of these cells, EBV eventually enters the resting B-cell memory compartment. Only EBNA-1 is expressed in these cells. The EBV growth-promoting latent genes are not expressed, and so the cells are not pathogenic. The limited repertoire of gene products also prevents frequent viral replication. Because cytotoxic responses to EBNA-1 are rare, EBNA-1-expressing lymphocytes escape immune surveillance. This then constitutes the viral reservoir. Intermittently, these cells may enter the lytic cycle during which viral replication occurs and is accompanied by suppression of host protein synthesis with subsequent lysis/death of infected cells, releasing virions to infect more cells. With immune suppression, latently infected cells in the peripheral blood or persistently infected cells on the oropharynx increase in number. The final mandate of the virus in achieving oncogenecity is to activate intracellular signaling involved in control of proliferation. This is achieved through diverse virally expressed genes that stimulate multiple intersecting cellular transduction pathways as discussed earlier.

Years after primary EBV infection, malignancies such as Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkin's disease can emerge. These tumors can initiate from a clone of EBV-infected cells. The role of EBV in these late-onset malignancies is complicated. Because EBV is clonal, it clearly sets the stage for progression to frank tumor. However, other factors may be important: specific failure of immune recognition; stimulation of B-cell proliferation by other infections; and/or appearance of secondary genetic aberrations or mutations.

EBV-Associated Cancers

Since its discovery as the first human tumor virus, EBV has been implicated in the development of a wide range of cancers (Table 4).

Burkitt's Lymphoma

Burkitt's lymphoma is a particularly aggressive lymphoma, the hallmark of which is a chromosomal translocation between chromosome 8 and either chromosomes 14, 2, or 22 (132–136). Because of this translocation, the oncogene *c-myc* (chromosome 8) is juxtaposed to the immunoglobulin heavy-chain (chromosome 14) or light-chain genes (chromosomes 2 or 22). This aberrant configuration results in the deregulation of *c-myc* expression. The relationship between EBV, Burkitt's lymphoma, and the *c-myc* translocation is complicated by the existence of two types of Burkitt's lymphoma: endemic (EBV present) and nonendemic (EBV generally absent). Although both types of Burkitt's lymphoma exhibit a *c-myc* translocation, the breakpoints within the genes involved differ and presumably the mechanism mediating juxtaposition differs as well (15).

Endemic Burkitt's lymphoma occurs primarily in equatorial Africa and Papua New Guinea, with EBV being discerned in >90% of cases (137). The role of EBV in Burkitt's lymphomas is strongly supported by observations of the Akata Burkitt's lymphoma cell line. Akata subcultures that have lost EBV have decreased growth and will not induce tumors in mice (138). Reinfection of the Akata cells with EBV reestablishes the malignant phenotype (139). Latency I gene expression is observed. It has been theorized that B-cell stimulation caused by continuous reinfection by malaria may contribute to an expanded number of EBV-infected, proliferating B cells, which have a higher probability of harboring cytogenetic abnormalities such as the t(8;14) (140). The breaks in chromosome 8 generally occur outside the *c-myc* locus. Whether there is a direct causal relationship between EBV and the development of the translocation is not known. There are several other mechanisms by which EBV may mediate lymphomagenesis. For instance, EBV modulates caspace-8 and FLICE-inhibitory protein, which leads to impairment of the Fas-mediated apoptotic pathway (141). Furthermore, EBV is responsible for increasing levels of the antiapoptotic protein BCL-2 in lymphoblastiod cell lines that maintain latency I (142).

Nonendemic Burkitt's lymphoma is found in the West and has been a rare disorder, but its incidence has increased dramatically because of its high prevalence in AIDS patients. Only

15–30% of nonendemic Burkitt's lymphoma cases are associated with EBV in the United States (143). However, the percentage of nonendemic disease harboring EBV is 85% in Brazil (144). As with malaria in endemic Africa, coinfection is thought to increase the oncogenic potential of the B cell (144). A t(8;14) translocation occurs in nonendemic Burkitt's lymphoma but, unlike the endemic form, the breaks in chromosome 8 appear 5′ to the first noncoding *c-myc* exon within the first exon or within the first intron of *c-myc* (15).

There are subtle phenotypic differences between endemic and nonendemic Burkitt's lymphoma. Bone marrow is less frequently involved in endemic disease, and patients are more sensitive to chemotherapy (145, 146). Also, the tumors isolated from nonendemic Burkitt's lymphoma patients are usually from different stages of B-cell development than those isolated derived from patients with endemic Burkitt's lymphoma (53). This phenomenon is reflected in the distinct breakpoints that occur in the immunoglobulin gene, presumably because the normal maturational rearrangement cascade was disrupted at different points (147). Regardless, the end result in both disorders is the deregulation of *myc* expression because of its juxtaposition to immunoglobulin enhancer regions. The relationship between the phenotypic distinctions and the presence/absence of EBV and/or molecular differences is currently not clear.

Hodgkin's Disease

Hodgkin's disease is characterized by an expansion of Reed-Sternberg cells, which are now postulated to be of B-cell lineage. Several lines of evidence link EBV to Hodgkin's disease: (*a*) a 4-fold increase in risk in individuals with a past history of infectious mononucleosis (148); (*b*) increased antibody titers to EBV viral capsid antigen (149); and (*c*) the detection of monoclonal EBV episomes in Hodgkin's-Reed-Sternberg cells (150).

The role that EBV plays in Hodgkin's disease is still not fully understood. EBV gene expression follows the latency II pattern with EBNA-1, LMP-1, LMP-2A and LMP-2B, and the EBERs being expressed. The questionable role of EBNA-1 in carcinogenesis and the oncogenic capabilities of LMP-1, LMP-2A and LMP-2B, and the EBERs have been addressed above. Interestingly, although LMP-1 and LMP-2 are both expressed, there seems to be no mounted CTL response to the Hodgkin's-Reed Sternberg cells (151–153). The role of IL-10 in the immortalization process and immune evasion remains a matter of debate (154). It is known that IL-10 suppresses the CTL immune response mediated by IFN-γ and IL-2 production by the Th-1 subset of T-helper cells and that cells producing IL-10 can escape immune surveillance (155, 156). Even so, it has recently been reported that *in vitro*, IL-10 did not inhibit Hodgkin's-Reed-Sternberg target cell lysis by preactivated CTL clones; in fact, IL-10 pretreatment of effector cells increased the levels of killing observed in some cases (154).

Not all subtypes of Hodgkin's disease harbor EBV to the same degree. EBV positivity in lymphoma tissue is discerned in ~70% of mixed cellularity Hodgkin's disease, >95% of lymphocyte-depleted Hodgkin's disease, and 10–40% of nodular sclerosis; the lymphocyte-predominant Hodgkin's disease subtype is almost always EBV negative (157). Geographic variations of EBV positivity have also been studied. EBV positivity in Hodgkin's disease is found in 65% of cases in Japan, 67% of cases in Mexico, 94% of cases in Peru, 40% of cases in Costa Rica, 92% of cases in Kenya, 41% of cases in Italy, and ~50% of cases in the United States (158–163). Strain variation does not seem to be a factor in EBV positivity; however, there is an increased incidence of EBV-2-positive Hodgkin's disease in immunocompromised individuals (164, 165). There is also data that suggests that the incidence of EBV-positive Hodgkin's disease is age-related, with the virus being preferentially associated with tumors from pediatric and older patients (166–170). Although primary EBV infection might account for the incidence of EBV positivity in young children, the association of EBV with this tumor in older patients may be attributable to increased viral activity as a consequence of flagging T-cell immunity.

Non-Hodgkin's Lymphoma in Immunocompetent Individuals

EBV is known primarily for its ability to infect B cells, but it can also infect other cells. Several types of non-B-cell, non-Hodgkin's lymphoma are associated with EBV (171, 172). This review will focus on the two types in which EBV has been most directly inplicated: nasal T/natural killer cell lymphoma and angioimmunoblastic lymphadenopathy.

Nasal T/natural killer non-Hodgkin's lymphoma cells exhibit several unique genotypic and phenotypic features. These features include an absence of T-cell antigens, expression of natural kiler cell marker CD 56, and absence of T-cell receptor gene rearrangement (15, 173–177). Clinically, these tumors occur in the nasal and upper aerodigestion area. EBV is consistently associated with these lymphomas, regardless of geographical location (163, 171, 178–189).

Angioimmunoblastic lymphadenopathy is a peculiar T-cell lymphoma in which expanding B-cell clones are often present beside the T-cell clones. EBV infection is seen mainly in the B lymphocytes and B immunoblasts, although the virus also occurs in rare neoplastic and nonneoplastic T cells (172). The presence of EBV in only a subpopulation of cells suggests that EBV infection is secondary to malignancy or that the viral genome has been lost from the malignant cell. EBV-positive B cells have also been observed growing in peripheral T-cell lymphomas (190). This raises questions about the possible activation of EBV in latently infected B cells by the neoplastic T cells, and/or the role of the EBV-positive B cells in maintaining the malignant T-cell process (191, 192).

Nasopharyngeal Carcinoma

Undifferentiated nasopharyngeal carcinoma is associated with EBV, whereas the association with the other two subtypes of nasopharyngeal cancer is controversial at best (193, 194). Undifferentiated nasopharyngeal cancer affects mostly individuals in their mid-40s and is more common in men (194). Nearly every undifferentiated nasopharyngeal carcinoma is EBV positive, regardless of geographical origin (195–198). Undifferentiated nasopharyngeal carcinoma is rare in most parts of the world, but there is an exceptionally high prevalence of this cancer in the Chinese province of Canton, Hong Kong, Taiwan, and among the Inuits in Alaska and Greenland (197, 199–203).

Indeed, in Taiwan, nasopharyngeal carcinoma is the most common cancer in men and the third most common in women (201, 202). The epidemiological pattern may be because of genetic susceptibility correlated with certain Chinese-related HLA antigen profiles and/or to environmental factors (the consumption of salted fish or exposure to fumes, smoke, and chemicals from the occupational environment; Refs. 197, 204–211).

In undifferentiated nasopharyngeal carcinoma, EBV infects the epithelial cells of the posterior nasopharynx in Rosenmuller's fossa in Waldeyer's ring (147, 212). There have been two models to explain infection of these cells by EBV. Although an EBV-compatible receptor on epithelial cells has not been found, a surface protein that is antigenically related to the B cell. CD21 receptor has been described and could conceivably be used as a point of entry by EBV (213). Alternatively, it has been suggested that EBV may gain entry into nasopharyngeal cells through IgA-mediated endocytosis (214).

The EBV genomes present in the epithelial cells of the nasopharynx are of clonal origin, and EBV is absent from surrounding tissues and invading T lymphocytes (147, 215). EBV has also been detected in *in situ* nasopharyngeal carcinoma, a precursor of undifferentiated nasopharyngeal carcinoma (216). These findings suggest that EBV infection occurs before neoplasia and is necessary for the progression of the malignant phenotype.

EBV-1 and EBV-2 have both been implicated in nasopharyngeal carcinoma. The majority of nasopharyngeal carcinoma cases from peoples in southern China, Southeast Asia, the Mediterranean, Africa, and the United States are associated with EBV-1 infection (217). Oddly, cases involving Alaskan Inuits are almost always EBV-2 related but contain polymorphisms characteristic of Asian EBV-1 (217). EBV undergoes latency II expression in undifferentiated nasopharyngeal carcinoma (216, 218–223). There is also a cytogenetic abnormality associated with undifferentiated nasopharyngeal carcinoma, a nonrandom deletion of the short arm of chromosome 3 at loci 3p25 and 3p14 (224, 225). The mechanism by which these deletions occur has not yet been determined.

One of the major questions surrounding undifferentiated nasopharyngeal carcinoma is how the EBV-infected cells can escape the immune response. Nasopharyngeal carcinoma cells possess normal antigen processing and are effectively recognized by EBV-specific CTLs, yet they are not destroyed (226). EBV-encoded viral IL-10 is increased in nasopharyngeal carcinoma and has been associated with increased production of IL-1α and IL-1β by epithelial cells and by CD4+ T cells, which may, in turn, contribute to the growth of the tumor and to immune evasion (227). Overexpression of bcl-2 may also play a role in oncogenesis by allowing the cell to bypass apoptosis (228, 229).

Gastric Carcinoma

EBV presence varies from >90% in lymphoepithelioma-like gastric carcinomas to between 5 and 25% in gastric adenocarcinomas (232–244). Whether EBV plays a pathogenic role in either of these two tumors is still unclear (233–241).

Given the morphological similarities between lymphoepithelioma-like gastric carcinoma and undifferentiated nasopharyngeal carcinomas, it has been proposed that in lymphoepithelioma-like gastric carcinoma, EBV spreads from the nasopharynx to the stomach (243, 244). In regard to gastric adenocarcinomas, EBV may enter the gastric epithelium without the use of a receptor. It has been suggested that this is accomplished by the binding of IgA antibody with EBV particles derived from B lymphocytes and the uptake of these particles by gastric epithelial cells (239). Alternatively, EBV may enter the gastric epithelial cells via a receptor other than the CD21 receptor (245).

EBV exhibits a novel latency pattern in gastric adenocarcinomas that includes the production of BARF-1, a homologue to human colony-stimulating factor 1 receptor and intracellular adhesion molecule 1, and the absence of LMP-1 (125, 246–248). Although any mechanism relating EBV to tumorigenesis in gastric malignancies remains highly speculative, it has been demonstrated that there is a delay in apoptosis in EBV-positive gastric carcinomas (associated with up-regulation of BCL-2 and p53) and a decrease in cellular differentiation (associated with decreased E-cadherin expression; Refs. 244, 248–251).

Breast Cancer

The relationship between EBV and breast cancer is controversial. Some studies have reported an EBV incidence in breast cancer tissue as high as 21–51% (252–254), whereas other investigators have failed to detect EBV in any breast cancer tissue samples (255–257).

Why is EBV reported in some studies and not in others? Possible reasons include: (*a*) distinct EBV detection techniques; (*b*) differing EBV-derived proteins or RNAs analyzed; and (*c*) epidemiological variation in EBV infections or in breast cancer itself. Regardless, whether EBV is present in breast cancer and its possible etiological role in oncogenesis remain to be clarified.

Leiomyosarcomas

Leiomyosarcomas are smooth muscle tumors. They are not associated with EBV in immunocompetent hosts but have been strongly correlated with viral infection in patients whose immune system is compromised by HIV or other factors (280). These observations also indicate that EBV is capable of infecting smooth muscle cells, a finding consistent with experimental evidence that the EBV receptor is present on those cells (280).

EBV-Associated Lymphomas in Immunocompromised Individuals

There exist several distinct classes of EBV-associated lymphoproliferative disorders in immunocompromised individuals. First, there is a disorder resulting from an inherited immunodeficiency known as X-linked lymphoproliferative disorder. Second, there are lymphomas associated with immunosuppressive drugs given to transplant recipients. Finally, there are AIDS-related lymphoproliferative disorders. The most common gene expression pattern in these disorders is latency III. For the most part, EBV-associated lymphomas in the immunocompromised host are aggressive and difficult to treat.

X-Linked Lymphoproliferative Disorders. X-Linked lymphoproliferative disease is characterized by three major phenotypes: fatal or fulminant infectious mononucleosis, B-cell

lymphomas, and dysgammaglobulinemia. Most of the lymphomas are extranodal, usually of the Burkitt type, and they often involve the intestine (258, 259). Death (which is virtually universal by age 40) is generally because of hepatic necrosis and bone marrow failure secondary to an uncontrolled cytotoxic T-cell response. A central paradox concerning the etiology of X-linked lymphoproliferative disorder lies in the fact that until recently, EBV infection was believed to be the trigger for immune dysregulation. However, it is now apparent that patients seronegative for EBV can exhibit the X-linked lymphoproliferative disorders and that lymphomas can predate EBV infection.

The gene responsible for this disorder has been mapped to the long arm of the X chromosome (Xq24) and it designated SH2D1A/SAP (263, 264). This gene is important in T/B-cell homeostasis after viral infection. In particular, defects in this gene may lead to a decreased ability to control immune responses to viruses, including EBV (259).

Posttransplant Lymphoproliferative Disorders. These heterogeneous lymphoproliferative disorders arise in the setting of therapeutic immunosuppression after organ transplantation (129). Nearly all forms of the disorder harbor EBV, and these lymphomas tend to be aggressive. Their development is probably a multistep process. Iatrogenic immunosuppression leading to primary EBV infection or reactivation of latent EBV infection is followed by polyclonal expansion of B-cell populations with a selective growth advantage. These cells are susceptible to genetic changes and BCL-6 may be one of the first such genes altered (268, 274). Subsequently, other molecular aberrations emerge and drive malignant growth (reviewed in Ref. 268).

The incidence of posttransplant lymphoproliferative disorders ranges from 0.5 to 30% and varies greatly depending on the organ being transplanted, the EBV status of the transplant recipient and donor, and the therapies used to achieve immunosuppression (268–276). EBV seronegativity at the time of transplant and pediatric age are predisposing factors. The disorder occurs commonly in combined liver-kidney transplants, followed by cardiac, liver, lung, and then kidney transplants. Constitutional factors such as cytokine gene polymorphism may play a predisposing role as well. In addition, intensity of immunosuppression, receiving T-cell-depleted marrow and concurrent cytomegalovirus may be important.

A variety of distinct posttransplant lymphoproliferative disorders have been described and include plasmacytic hyperplasia, polymorphic lymphoproliferative disorder (encompassing polymorphic B-cell hyperplasia and polymorphic B-cell lymphoma), malignant non-Hodgkin's lymphoma, and multiple myeloma (268, 273). Most posttransplant-lymphoproliferative disorders (PTLDs) are B-cell neoplasms. PTLDs arising in bone marrow transplant recipients are generally of donor origin, whereas those in solid organ recipients are usually of recipient origin. Molecular testing is increasingly important in the diagnosis and monitoring of patients affected by these diseases (132, 268). There appears to be a correlation between PTLDs and EBV viral load measured by quantitative PCR of the peripheral blood. In biopsy tissues, molecular detection of EBER transcripts by *in situ* hybridization remains the gold standard for proving that a histopathological lesion is EBV related. EBER hybridization and EBV-LMP-1 immunostains are used routinely to detect latent EBV in tissues affected by PTLD. The initial treatment of PTLD is reduction of immunosuppression. Antiviral agents, IFN, monoclonal antibodies, cell-based therapy, and chemotherapy have also been used.

AIDS-Related Lymphoproliferative Disorders. AIDS-related lymphoproliferative disorders are a heterogeneous group of diseases that arise in the presence of HIV-associated immunosuppression, a state that permits the unchecked proliferation of EBV-infected lymphocytes. These aggressive disorders include both central nervous system and systemic lymphomas. Pleural effusion lymphomas also occur and often contain EBV in addition to human herpesvirus 8.

AIDS-related central nervous system lymphomas are derived from germinal center B cells and almost always contain EBV (129). The central nervous system lymphomas include immunoblastic and large noncleaved lymphomas. The immunoblastic subtype expresses LMP-1 and BCL-2 but not BCL-6. The large noncleaved subtype express BCL-6 but not LMP-1 or BCL-2 (277).

The AIDS-related systemic lymphomas are comprised of several subtypes, including diffuse large cell lymphomas, immunoblastic lymphomas, Burkitt's lymphomas, and small, noncleaved Burkitt's-like lymphomas. EBV positivity for these lymphomas ranges from 30 to >90% (129, 278–283).

Treatment

Despite our growing understanding of the role of EBV in the pathogenesis of disease, the optimal management of EBV-associated tumors remains unsatisfactory. Exploration of antiviral agents, immune-based therapies, and specific monoclonal antibodies is, however, proceeding with encouraging results (286–299). In the posttransplant setting, EBV-related lymphomas can also be managed by reducing the level of immunosuppression, although this strategy may threaten the integrity of the transplant.

Antivirals. There are several antiviral compounds that have entered the clinical setting and have some anti-EBV activity. However, it has been difficult to demonstrate reproducible antitumor effects and, to date, reports of tumor regression remain anectodal.

The majority of these drugs are broad-spectrum antiherpesvirus and anticytomegalovirus agents that vary in their effectiveness against EBV. They include ganciclovir, famcyclovir, acyclovir, valaciclovir (a prodrug of acyclovir), foscarnet, and cidofovir. Acyclovir and ganciclovir are not drugs of choice because, in EBV-associated lymphoid disorders (in contrast to the situation in EBV lytic disease), the virus is not replicating lytically, and the viral thymidine kinase enzyme is not expressed. (These pharmacological agents are nucleoside analogues, which are converted by thymidine kinase to their monphosphate form and then by cellular enzymes to active triphosphates. The toxic metabolites are incorporated into DNA, leading to premature strand termination and apoptosis.) To circumvent this problem, arginine butyrate, which can selectively activate EBV thymidine kinase genes in lymphoma cells, has been administered together with gancyclovir; this combination has demonstrated some efficacy in patients with EBV-

associated lymphoproliferations after solid organ transplantation (286).

The action of foscarnet is directed against viral DNA polymerase, independent of the presence of viral thymidine kinase. There are isolated reports of complete remission in patients with EBV-associated lymphoproliferations (295). Cidofovir is also active against EBV DNA polymerase and is a potent inhibitor of EBV replication *in vitro*; it has striking antitumor effects in nasopharyngeal xenografts (285), which, however, appears to be unrelated to inhibition of viral DNA polymerase. Cidofovir can also induce regression of oral hairy cell leukoplakia (a condition characterized by intense EBV replication in oral epithelium of patients with immune compromise, generally because of AIDS; Ref. 296). Taken together with the anti-CD20 monoclonal antibody known as Rituximab, cidofovir can produce complete remission of CD20-expressing, posttransplant lymphoproliferative disorders (284). Of interest, although not classically thought of as an antiviral agent, hydroxyurea is known to eradicate extrachromosomal DNA elements and has been used successfully, albeit anecdotally, to treat AIDS-related central nervous system lymphoma (288).

Azelaic bishydroxamic acid, a histone deacetylase inhibitor, kills EBV-positive lymphoblastoid cell lines at low doses (287). Zidovudine, an antiretroviral agent used to treat HIV, when combined with IFN-α, can induce apoptosis (*in vitro*) of EBV-positive lymphoma cells from AIDS patients (296). A variety of nonconventional compounds may have antiviral effects, too. For instance, flavanones (amorilin and lupinifolin) from plant extracts block EBV early antigen activation *in vitro* (289). Additionally, flavonoid derivatives synthesized from morin and quercetin and several herbal remedies may have varying degrees of anti-EBV activity (290, 291).

Immunotherapy. The drawback to antivirals is that they have no influence on the underlying immunosuppression that favors EBV-driven tumorigenesis. Adoptive immunotherapy using EBV-specific CTLs, although time consuming and work intensive, may overcome this disadvantage (292). The CTLs can be taken from a donor and infused directly into the patient or expanded *in vitro* and then infused to reestablish immunocompetence. Generation of EBV-specific CTLs from seropositive healthy donors generally takes ~8–12 weeks. This method can be used as prophylaxis or to eradicate established disease in recipients who develop lymphoproliferative disorders after allogeneic hematopoietic stem cell transplants (292). These types of disorders are a particluarly good target for such CTL therapy because the transformed cells, which are generally of donor origin, express all latent cycle virus-associated antigens.

In recipients of solid organ transplants who develop EBV-associated lymphoproliferative disorders, donor-derived T cells may be of limited value because the tumor almost always arises in recipient B cells. Unmanipulated allogeneic T cells from an HLA-matched sibling have been successfully used (reviewed in Ref. 292). Autologous and haploidentical EBV-specific CTLs have also been administered. However, harvesting autologous CTLs may often be impractical or impossible. Alternatively, a panel of CTLs grown from healthy donors can be generated, and those CTLs that are HLA-matched can be infused (297).

For other (nontransplant) EBV-related malignancies, there is only limited clinic experience with EBV-specific CTLs. For the most part, this experience has been in Hodgkin's disease. To date, complete responses have not been achieved (reviewed in Ref. 292).

Because donor CTLs may be alloreactive, potential hazards of adoptive immunotherapy include graft-*versus*-host disease. In addition, tumor resistance may occur because of mutations in EBV epitopes recognized by CTLs or by other mechanisms (*e.g.*, production of cytokines such as IL-10) exploited by the tumor to evade surveillance (299).

Efforts are also underway to develop an EBV vaccine either to protect against initial infection or to boost immunity in individuals with EBV-related tumors. The vaccines currently under investigation are using combinations of several defined EBV epitopes to induce EBV-specific CTL immunity (293). Finally, there is the possibility of using gene therapy vaccine vectors in which numerous, linearly joined EBV-specific epitope sequences are expressed as polypeptides and presented for CTL recognition and induction of EBV-specific CTL immunity (294).

Monoclonal Antibodies. The anti-CD20 monoclonal antibody designated Rituximab has enjoyed significant success in the treatment of a variety of CD20-expressing lymphomas. It is also an effective agent in the management of EBV-related lymphoproliferative disorders. A response rate of 69% (mostly complete responses) has been reported in a group of transplant recipients (either solid organ or hematopoietic stem cell transplant; Ref. 298). Because these lymphomas use IL-6 as a growth factor, anti-IL-6 monoclonal antibodies have also been tried. The reported response rate was 67% (8 of 12 patients treated; Ref. 299).

In summary, therapy for EBV-associated tumors remains largely in the nascent stages, but research is being fueled by the successful development of new antiviral and immunological approaches. To date, antiviral agents have received only perfunctory consideration, perhaps because of uncertainty regarding the role of EBV in maintaining established cancers. However, recent studies suggest that selected antiviral compounds, as well as therapeutic strategies such as use of adoptive immunotherapy with EBV-specific CTLs or administration of targeted monoclonal antibodies, hold considerable promise for the treatment of EBV-related malignancies.

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