The contribution of ebv to the pathogenesis of classical hodgkin lymphoma

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Hodgkin lymphoma (HL) exists in two major forms, the so-called classical type (cHL) and the nodular lymphocyte predominant type (NLPHL). Since NLPHL is considered to be an EBV-negative entity, this review focusses only on the cHL form. Although cHL is a curable disease in many cases, we still lack an understanding of its pathogenesis that could lead to kinder treatments for patients, and also to more effective therapies for the smaller subset of patients who are destined to die of their disease. One approach might be to therapeutically target the Epstein-Barr virus (EBV), which is present in up to one-half of cases in resource rich nations, and in almost all cases in some resource-poor countries. However, it has been suggested that EBV might be simply a silent passenger in cHL. In this review, we present evidence in support of a crucial role for EBV in virus-positive cHL. In particular, we highlight important epidemiological differences between EBV-positive and EBV-negative cHL that suggest different aetiologies, as well as genetic differences, including a different profile of somatic mutations pointing to a distinct contribution for EBV in substituting for cellular genetic changes that are required for disease development when the virus is absent. We also focus attention on important roles for the individual latent virus genes in the pathogenesis of cHL. Overall, this review suggests that a better understanding of how EBV contributes to the pathogenesis of cHL may eventually lead to improved stratification of patients and to the development of therapies that specifically target EBV or its latent genes.

Keywords: Hodgkin lymphoma; Epstein-Barr virus (EBV); transformation

Introduction

The oncogenic Epstein-Barr virus (EBV) is present in a subset of cases of classical Hodgkin lymphoma (cHL). Despite growing evidence of its importance in the pathogenesis of the subset of virus-associated cHL, therapies that specifically target EBV are lacking. We believe it is now timely to revisit the contribution of EBV to the pathogenesis of cHL, particularly with respect to the role of the viral latent genes, some of which are now being explored as targets of new drug and immunotherapeutic approaches.

General features and pathogenesis of HL

Hodgkin lymphoma (HL) has an incidence of around

3/100,000 per year. Lymph nodes are the most often affected tissues, although extranodal disease does occur. Affected tissues show effacement of existing structures which are replaced by rare malignant cells, surrounded by a florid reactive infiltrate. Based on differences in histology and immune phenotype, HL can be classified into two major types; these are classical HL (cHL) and nodular lymphocyte predominant (NLP) HL (1). The malignant cells of cHL are known as Hodgkin/Reed-Sternberg (HRS) cells, and those of NLPHL as lymphocyte predominant (LP) cells. There are four major subtypes of cHL, known as mixed cellularity, nodular sclerosis, lymphocyte rich and lymphocyte depleted HL. The tumour cells of HL are derived from mature B lymphocytes (2), and display evidence of somatic hypermutation indicating that they develop from germinal centre, or more likely, post-germinal centre B cells (2-5). In approximately one-quarter of cases of cHL, the immunoglobulin genes have so called 'crippling' mutations which prevent proper expression of surface immunoglobulin (3). In fact it is now believed that the loss of B cell receptor (BCR) functions is probably directly involved in the pathogenesis of most, if not all, cases of cHL.

Most B cells require signalling through the BCR for their survival, yet HRS cells do not appear to need these survival signals. These observations suggest that a crucial event must be the acquisition of mechanisms that prevent the apoptosis that would be the normal fate of germinal centre B cells lacking a functional BCR. Multiple cell signalling pathways are aberrantly activated in HRS cells, many of which contribute to this anti-apoptotic phenotype. For example, HRS cells display constitutive activation of a family of transcription factors known as nuclear factor kappa B (NF-κB) (6). Inhibition of NF-κB signalling in HL cell lines increases their sensitivity to apoptosis and impairs tumourigenicity in severe combined immunodeficiency mice (7,8). HRS cells express multiple tumour necrosis factor receptors, including CD30, CD40, TACI, BCMA and RANK which can induce the activation of NF-κB signalling following their engagement with ligands expressed on immune and other cells of the tumour microenvironment (TME) (9,10). Constitutive NF-κB activation can also be caused by different genetic lesions in HRS cells, including amplification of the gene encoding the c-REL subunit of NF-κB, (11-13), mutations in genes encoding inhibitors, IκB alpha and IκB epsilon (14-18), and TNFAIP3/A20, a ubiquitin modifying enzyme that inhibits NF-κB signalling (19).

The JAK/STAT signalling pathway is also critically involved in cHL pathogenesis and may be activated via the cytokines which are produced either by HRS cells or by cells of the TME; this in turn elevates the levels of phosphorylated forms of STATs (e.g., STAT3, STAT5A and STAT6) (20-22). JAK/STAT signalling can also be aberrantly stimulated by genetic lesions such as the amplification of JAK2 or loss-of-function mutations in SOCS1 and PTPN1/PTPB1 which are negative regulators of these pathways (23-25).
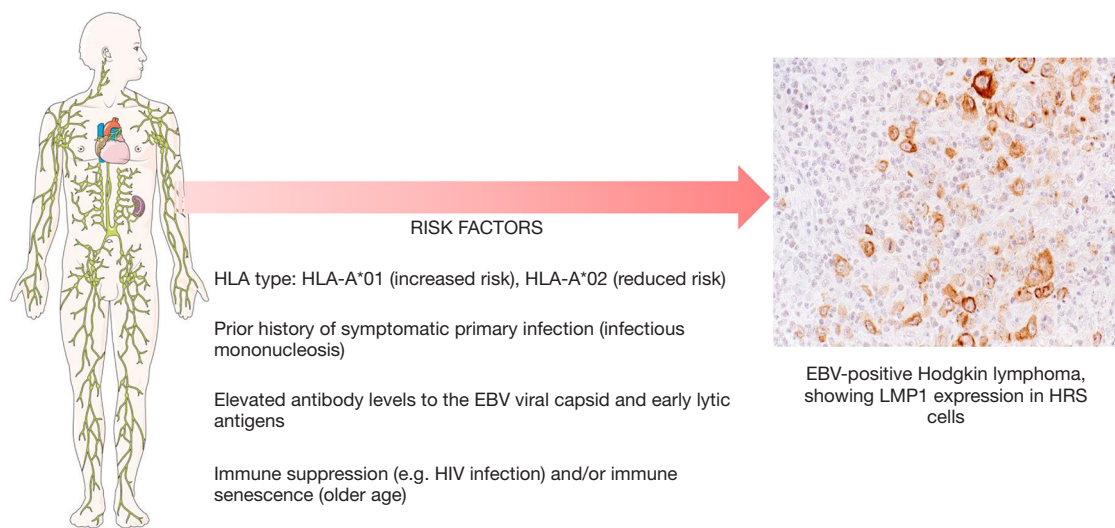
Identification of EBV in cHL

EBV was initially suggested to be involved in the pathogenesis of cHL after it was shown that patients had raised antibody levels to EBV antigens in their blood (26). Moreover, elevated levels were also shown to be present in patients before the onset of cHL (27).

Southern blotting for EBV DNA was first used to identify the presence of EBV DNA in the tissues of cHL patients (28). EBV was localized to HRS cells using the anti-complement immune fluorescence assay (29), by in situ hybridization (ISH) for EBV DNA (30,31), and by ISH for two RNA species known as Epstein-Barr virus encoded RNAs (EBER1 and EBER2) (32). An aetiological role for EBV in cHL was supported by the detection of viral genomes bearing identical fusion sequences in biopsies. These sequences are created when the circular genomes are formed from linear virus DNA and are unique to a single infection event. Thus, monoclonal viral genomes present in cHL indicate that infection is an early event (30). EBV is consistently retained during disease progression, suggesting it is required for maintenance of the tumour phenotype (33).

Epidemiology of EBV-associated cHL

EBV is associated with cHL, but not with NLPHL. However, not all cases of cHL are EBV-positive. Moreover, the proportion of positive cases varies within different populations (34,35). Thus, in resource-rich nations, EBV-positive rates range between 20% to 50%; here more EBV-positive cases are seen in older people and in children, and fewer in young adults (36,37). In contrast, EBV positive rates are often substantially higher in resource-poor countries (38,39). EBV-positive disease is more common in males, in patients with mixed cellularity disease, and in some ethnic groups, even when taking into account potential confounding factors, such as socioeconomic status (40).

RISK FACTORS

HLA type: HLA-A*01 (increased risk), HLA-A*02 (reduced risk)

Prior history of symptomatic primary infection (infectious mononucleosis)

Elevated antibody levels to the EBV viral capsid and early lytic antigens

Immune suppression (e.g. HIV infection) and/or immune senescence (older age)

EBV-positive Hodgkin lymphoma, showing LMP1 expression in HRS cells

Figure 1 Risk factors for the development of EBV-positive classical Hodgkin lymphoma.

The incidence of EBV-positive cHL is also more common in HIV-positive individuals especially when the levels of immune impairment are at intermediate levels (41,42). Thus, declining levels of EBV-specific immunity in the early stages of HIV infection contribute to an increased risk of EBV-positive HL. However, this risk of developing cHL declines as CD4+ T cell numbers fall further, emphasising the importance of CD4+ T cells in the pathogenesis of cHL.

First degree relatives of patients with cHL patients have between a 3-fold and 9-fold increased risk of developing the disease (43,44), this rises to 100-fold for monozygotic twins compared with dizygotic twins (45). Susceptibility loci exist within the human leukocyte antigen (HLA) region (46,47); HLA-A*01 and HLA-A*02 alleles confer an increased and decreased risk of EBV-positive cHL, respectively (47-49) (*Figure 1*). These findings illustrate the potential importance of immune control of the virus in the pathogenesis of the EBV-positive form of cHL (50). A prior history of infectious mononucleosis (IM) is associated with an increased risk of developing EBV-positive, but not EBV-negative, cHL (51-53) and some of the same HLA associations are also observed for IM (*Figure 1*).

EBV potently transforms B lymphocytes *in vitro*

Before considering how EBV might contribute to the development of cHL, we briefly outline what is known about the transforming potential of EBV and how the virus might

interact with B cells in the normal asymptomatic host.

Infection of resting B lymphocytes by EBV *in vitro* can lead to their transformation, giving rise to continuously growing cell lines, referred to as lymphoblastoid cell lines (LCL). If lymphocytes from the blood are used, the T lymphocytes present must be depleted or suppressed by drugs such as cyclosporin A (54), demonstrating the importance of the T cell response in controlling EBV infection *in vivo*.

EBV encodes a small subset of its genes in the latency phase of the virus life cycle which is characterized by the absence of virus replication. These 'latent' genes include nuclear antigens, known as EBNAs (EBNAs 1, 2, 3A, 3B, 3C, EBNA-LP), latent membrane proteins (LMP1, LMP2), as well as two non-coding Epstein-Barr-encoded RNA (EBER1, EBER2), and viral miRNA (55,56). Some latent genes, for example, EBNA2 and LMP1 are necessary for the transformation of B cells, at least in the laboratory (57). Latency III is the term used to describe the type of latency displayed by LCL; here all known latent genes are present. Restricted forms of latency are observed during the 'normal' differentiation of EBV-infected B cells *in vivo*, as well as in EBV-associated malignancies, including cHL. EBV can also express 'lytic' genes when the virus shifts to its replicative cycle ending in the release of infectious virus particles.

EBV infection of B cells is characteristic of the asymptomatic carrier state

EBV has evolved to survive for the life-time of the
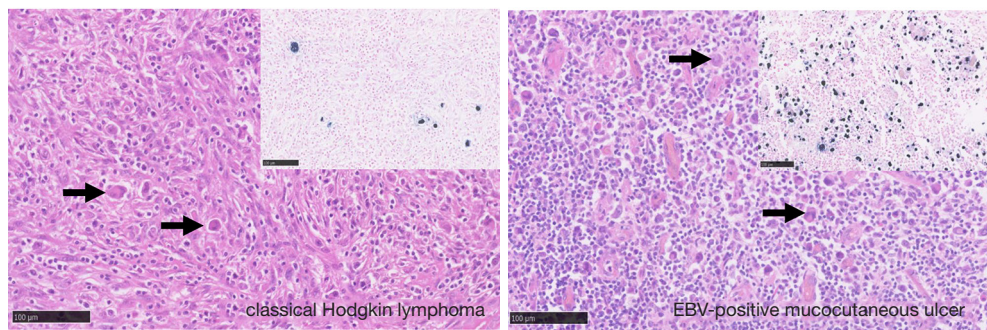
Figure 2 Morphology and EBER-positivity in classical Hodgkin lymphoma and EBV-positive mucocutaneous ulcer: HRS cells (cHL) and HRS-like cells (EBV + MCU) are arrowed. EBER staining is shown in the inset.

asymptomatic host, and does so using a highly evolved mechanism that relies on the colonisation of memory B cells (58). How EBV eventually gets into memory B cells has been difficult to fully define, mainly because primary infection itself largely goes unnoticed and when IM does occur after primary infection, by the time it becomes symptomatic, the early events in virus infection have already taken place. To further exacerbate an already difficult problem, the virus colonises only a minute fraction of B cells in asymptomatic carriers (perhaps as low as 1 in 10^6 B cells). Notwithstanding these difficulties, the favoured model of EBV persistence suggests that initial infection of B cells by EBV causes them to enter the cell cycle, and to express the latency III pattern of viral gene expression; in this respect the initially infected B cells are probably similar to LCL. These EBV-infected B cells may then adopt a phenotype more closely resembling a germinal centre (GC) B cell, this time they adopt a latency II programme in which EBNA1, but not the other EBNAs, and the latent membrane proteins are present (59). This pattern of virus expression mirrors that seen in cHL. At this stage, LMP1 and LMP2 provide the EBV-infected B cells with surrogate CD40 and B cell receptor (BCR) signals, respectively, and allow the EBV-infected GC B cells to survive and subsequently to differentiate into memory B cells (60,61). The EBV-infected memory B cells no longer express virus genes (a state known as latency 0), but can if necessary switch on EBNA1 expression to allow them to proliferate (this stage is known as latency I) (59). EBV-infected B cells can become plasma cells; in this case the lytic cycle is induced, eventually leading to virion release in oropharyngeal secretions. This is probably the major way in which the virus to transmitted from host to host (62).

It is important to also mention here that there is an alternative view of the establishment of the carrier state which is based on the observation that EBV-infected cells in GCs of patients with IM show evidence of somatic hypermutation, but without evidence of intra-clonal diversity; this means that these cells are no longer undergoing the hypermutation process (63,64). Moreover, LMP1 has been shown to be present in EBV-infected cells present outside the GC, potentially counteracting the argument that LMP1 is driving a GC reaction (65). Thus, this alternative model proposes that EBV directly infects memory B cells. Moreover, 'non-switched' memory B cells, which do not require GC activity can also harbour EBV (66-68). EBV infection can induce expression of activation-induced cytosine deaminase (AID) to stimulate somatic hypermutation (69).

EBV latent genes are important contributors to the pathogenesis of cHL

EBV-infected HRS cells express a restricted pattern of virus latency characterised by the presence of EBV's maintenance protein, EBNA1, as well as both latent membrane proteins. A subset of viral miRNA are also expressed. While the contribution of the EBV latent proteins to the pathogenesis of cHL is increasingly better understood (70), the roles of the EBV miRNAs have only just begun to be explored (*Figure 2*).

Epstein-Barr virus nuclear antigen-1 (EBNA1)

EBNA1 is essential for the maintenance of EBV episomes in infected cells, as it is a key viral replication factor and is responsible for tethering viral genomes to the chromosomes of the host cell; loss of EBNA1 expression therefore results

in the loss of EBV genomes during cell division (71). EBNA1 is also a transcription factor that can bind to viral and cellular promoters (72-74). EBNA1 inhibits TGFβ signalling, in part by modulating the levels of SMAD2. EBNA1 also decreases expression of the TGFβ target gene, PTPRK, which in turn promotes the growth and survival of HRS cells (75,76).

Latent membrane protein-1

LMP1 is a constitutively active homologue of CD40 that has been shown to activate NF-κB, JAK/STAT, AP-1 and phosphatidylinositol-3 kinase (PI3K)/AKT signalling (77-79). While LMP1 might be responsible for activating these pathways in EBV-positive cHL, mutations in components of these signalling pathways appear to be necessary when the virus is absent. For example, TNFAIP3 mutations are more commonly seen in EBV-negative cHL, suggesting that mutational inactivation of TNFAIP3 and EBV infection are alternative pathways both leading to deregulated NF-κB signalling (19). The requirement for more genetic changes in EBV-negative cHL is supported by other studies which show that EBV-positive cHL has significantly fewer chromosome abnormalities than EBV-negative cHL (80-82). LMP1 also induces many of the features of the aberrant transcriptional programme characteristic of HRS cells, including the down-regulation of BCR signalling components, and the increased expression of anti-apoptotic genes such as BCL2 and BFL-1 (83,84). The FLICE-inhibitory protein (c-FLIP), a negative regulator of Fas induced apoptosis (85), is also an LMP1 target and could be important in the rescue of pre-apoptotic GC B cells early in cHL pathogenesis (86). LMP1 also increases the expression of Programmed death ligand-1 (PD-L1) in B cells, which might account at least in part for the sensitivity of cHL to immune checkpoint inhbitors targeting the PD-L1/PD-1 axis, although definitive studies assessing the sensitivity of EBV-positive versus EBV-negative cHL to immune checkpoint blockade have not been done (87).

Latent membrane protein-2A (LMP2A)

EBV appears to be crucial for the survival of HRS progenitors harbouring so called 'crippling' mutations in immunoglobulin genes; these mutations are found almost exclusively in EBV positive cases (88). EBV efficiently immortalises BCR-negative GC B cells *in vitro*; an effect that is dependent upon LMP2A which provides a BCR-like signalling function (61,89). LMP2A also contributes

to the transcriptional programme of cHL, for example by reducing the expression of numerous B cell transcription factors, including EBF1 and E2A (90-93).

EBV-encoded miRNA

LCL express a subset of BART miRNA (including approximately half of Cluster 2) as well as 3 of the 4 BHRF1 miRNAs, that are subsequently turned off in GC B cells and memory B cells. In parallel, EBV-infected GC B cells and memory B cells up-regulate the remaining BART miRNAs by 5–10 fold (94). In EBV associated tumours expressing a latency II phenotype, including cHL, the latency III associated BART but not BHRF1 miRNAs are up-regulated (95). Among these, miR-BART2-5p is expressed in EBV-positive cHL and can act as an anti-sense miRNA to the EBV DNA polymerase BALF5 to inhibit virus replication (96). miR-BART2-5p also decreases BCR-mediated NF-kappa-B activation (97). miR-BART13-3p is one of the most highly expressed viral miRNA in cHL, and can be released into the circulation via exosomes (98). miR-BARTs in exosomes derived from EBV-positive cells have been shown to induce changes in the phenotype of macrophages, including the increased production of cytokines, such TNF-α, and IL-10 (99).

EBV also influences host miRNA expression in cHL. For example, Navarro *et al.* observed a subset of 10 host miRNAs whose expression was influenced by the presence of EBV. Among these, miR-96, miR-128a, miR-128b were selectively down regulated in EBV-positive cHL. The authors also reported a distinctive signature of 25 miRNAs that were differentially expressed between cHL and reactive lymph nodes. Interestingly, the dysregulation of miR-21 that favours cell survival by indirectly up-regulating anti-apoptotic genes suggests an important role for cellular miRNAs in the biology of cHL (100).

Co-expression of latent genes

A drawback of many of the studies investigating the function of individual virus genes has been the reliance on single gene over-expression or knockdown/knockout experiments; an approach that cannot take account of the effects of the co-expression of virus genes. This could be important, particularly because some studies have shown that some of the latent genes, for example, LMP1 and LMP2A have partially overlapping, as well as counteracting, transcriptional programmes (101). Moreover, it has been

shown that when expressed in the B cells of transgenic mice, LMP1 is transforming, but not when LMP2A is co-expressed (102). In another study it was shown that LMP1 and LMP2A co-expression in mouse B cells led to tumour development, but only if the animals were immunosuppressed, suggesting that a background of immune impairment is important (103). Studies exploring the co-expression of virus genes in cHL at single cell resolution are required.

EBV and the tumour microenvironment of cHL

The TME is a defining feature of cHL and there is some evidence that EBV is at least partly responsible for reshaping this TME through expression of the latent genes, and also potentially through limited induction of the lytic cycle. For example, LMP1 an increase production of a diverse array of different chemokines and cytokines (104,105). EBNA1 can also influence the transcription of genes encoding key soluble factors, for example the chemokine CCL20 which is important in the chemo-attraction of regulatory T cells (106). Conversely, the cHL TME of cHL could also modulate viral gene expression in tumour cells. A good example here is the expression of LMP1 which can be regulated by different cytokines (107,108). The TME could also modify EBV's oncogenic functions. For example, LMP1 can increase expression of discoidin domain receptor 1 (DDR1), a collagen receptor leading to the increased survival of lymphoma cells (109).

The function of EBV-specific T cells in the TME of cHL might be compromised by a variety of immune evasion mechanisms. Thus, loss of HLA expression is frequently observed in HRS cells, but is more commonly found in EBV-negative cHL (110-112); in some cases this is caused by inactivating mutations in the beta-2-microglobulin gene (113). EBV-positive cases of cHL usually express normal or sometimes higher levels of HLA expression, and contain more activated CTLs than EBV-negative cases (110-112,114). EBV-positive cHL also contains more NK cells (115). These data suggest that EBV utilises other mechanisms to evade anti-tumour immune responses in cHL, including the induction of immune checkpoint molecules, such as PD-L1 (87).

## Difficulties in the diagnosis of EBV-positive cHL

The diagnosis of cHL is dependent upon morphological evaluation by a haematopathologist who can recognize the typical HRS cell morphology and the characteristic cellular infiltrate supported by additional immunohistochemistry stains for example for recognition of CD30-positive HRS cells. However, a number of EBV-associated lymphoproliferative disorders (LPD) can harbour EBV-positive HRS-like B-cells, morphologically mimicking EBV-positive cHL. Many of these LPD show distinct clinical behaviour and require radically different management approaches from cHL, potentially leading to over- or undertreatment if not recognised by the pathologist. Whilst cHL is typically a nodal disease, extranodal extension can be seen in late stage disease (116). Furthermore, extremely rare manifestations of primary extra-nodal cHL have been described (117). Similarly, many of the mimics of EBV-positive cHL can present as nodal or extranodal disease and thus have to be considered in the differential diagnosis.

EBV-positive diffuse large B-cell lymphoma (DLBCL), NOS, is systemic lymphoma typically presenting with prominent extranodal involvement in the elderly, although younger patients can also be affected (118). EBV-positive DLBCL, NOS, can show large pleomorphic HRS-like lesional B-cells which can associated with a prominent inflammatory milieu. On immunophenotyping, CD30 expression is usually seen in the lesional cells and can co-exist with CD15 expression in 68% of cases (119). Expression of CD20 is an important marker in distinguishing EBV+ DLBCL, NOS, from EBV+ cHL. However, CD20 can show variable expression in EBV+ DLBCL, NOS, as over 50% of lesional cells are typically positive.

EBV-positive mucocutaneous ulcer (EBVMCU) is a localised ulcerating EBV-positive LPD affecting the skin or mucous membranes (120) (*Figure 3*). EBVMCU are usually solitary but multi-focal manifestations have been described (121). The lesions are typically associated with immunosuppression or in older patients, are assumed to be consequence of immunosenescence (120). EBVMCU is an indolent disease and usually resolves upon once the source of immunosuppression is removed. Rituximab has been used with some success in refractory cases.

Some lymphomas, not in themselves associated with EBV, can show EBV-positive HRS-like B-cells in the background. The archetypal example is angioimmunoblastic lymphoma (AIL), a T-cell lymphoma with a T-follicular helper(Tfh) cell phenotype (118). Up to 95% of AIL can show EBV+ B-cell blasts in the background. In some cases, the B-cell component in the background of AIL can progress to EBV+ DLBCL or EBV+ cHL (122). Other lymphomas accompanied by EBV+ B-cell blasts have also
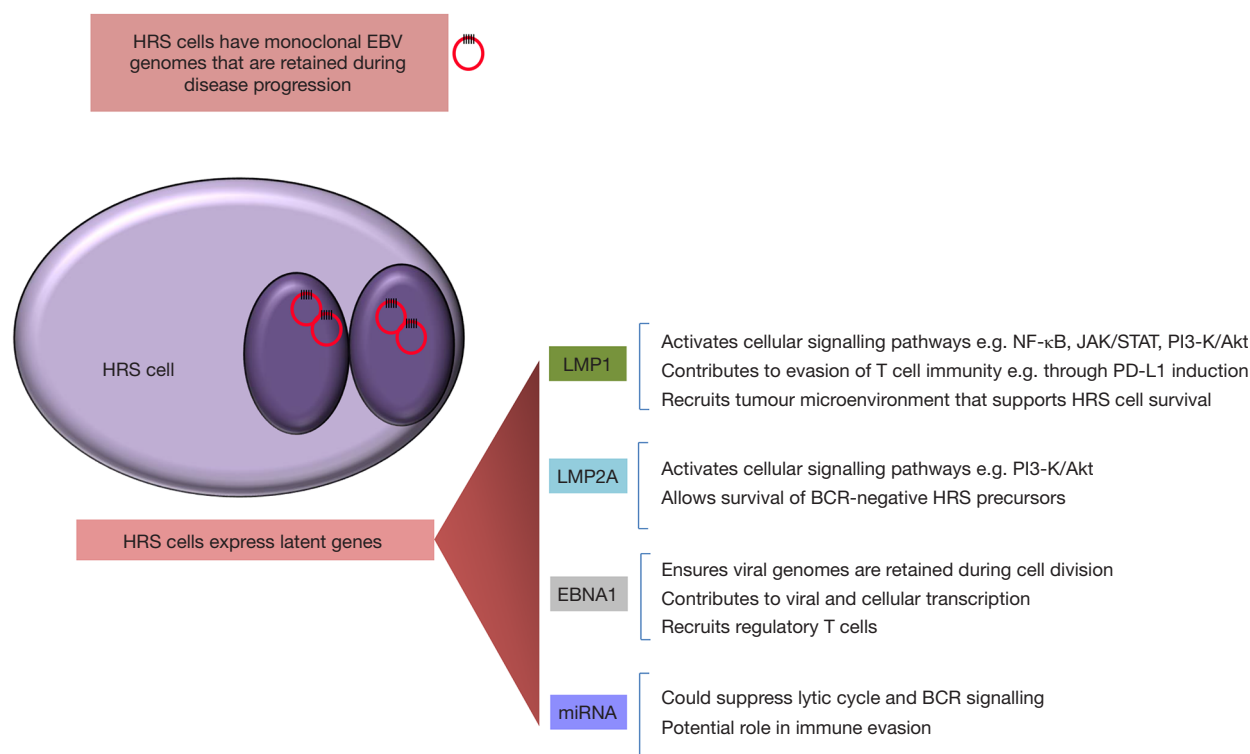
Figure 3 Contribution of EBV latent genes to the pathogenesis of classical Hodgkin lymphoma.

been described in the background of other EBV-negative lymphomas including chronic lymphocytic leukaemia and mantle zone lymphoma (123,124).

EBV-positive manifestations of lymphomas, traditionally considered not to be associated with EBV, have now been described, thus broadening the range of potential differential diagnoses. Rare examples of EBV-positive nodular lymphocyte predominant Hodgkin lymphoma, primary mediastinal B-cell lymphoma and EBV-positive mediastinal grey-zone lymphoma (PMGZL) (intermediate features between primary mediastinal lymphoma and Hodgkin lymphoma) have been described (125,126). The diagnosis of mediastinal grey-zone lymphoma is further complicated, as both cHL and PMGZL can occur in the same vicinity (composite lymphoma), or develop sequentially, where EBV status has been reported to change from the initial to subsequent biopsy. The diagnosis of these entities necessitates the presence of all the typical diagnostic features of the EBV-negative variant to be present in order to make the diagnosis. Nonetheless, the recognition of these entities can make distinction between the various EBV-positive LPD extremely difficult.

Concluding remarks

A subset of cHL patients harbor EBV in their tumour cells. Although the contribution of EBV to the pathogenesis of cHL has been debated, we argue that differences in the epidemiology, genetics, and biology of EBV-positive compared with EBV-negative cHL strongly suggest a key role for the virus. Notwithstanding debate over EBV's exact contribution to the oncogenic process in cHL, there is undoubtedly an opportunity to exploit the presence of EBV in tumours for patient benefit. In some LPD and in other EBV-associated tumours such as nasopharyngeal carcinoma, EBV detection in blood and other tissues can be a useful biomarker. However, as yet routine blood testing for EBV is not employed in the management of the majority of EBV-associated malignancies, including cHL. Moreover, the development of new approaches to specifically target EBV, for example, by reactivating the virus into the lytic cycle (and thereby killing the infected cell, or making it susceptible to drugs such as ganciclovir) (127-129), gene therapy (130), EBNA1 inhibitors (131,132), and therapeutic vaccination/T cell therapies (133,134) are provide exciting new opportunities to improve outcomes for patients.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Christopher P. Fox, Claire Shannon-Lowe) for the series "Lymphoma and Viruses" published in *Annals of Lymphoma*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aol-21-8). The series "Lymphoma and Viruses" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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