VIRUSES AND LYMPHOMAS

Contribution of the Epstein–Barr virus to the molecular pathogenesis of Hodgkin lymphoma

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Although the morphology of the pathognomonic Reed–Sternberg cells of Hodgkin lymphoma (HL) was described over a century ago, it was not until recently that their origin from B lymphocytes was recognised. The demonstration that a proportion of cases of HL harbour the Epstein–Barr virus (EBV) and that its genome is monoclonal in these tumours suggests that the virus contributes to the development of HL in some cases. This review summarises current knowledge of the pathogenesis of HL with particular emphasis on the association with EBV.

Hodgkin lymphoma (HL) is characterised by the disruption of normal lymph node architecture and the presence of a minority of malignant Hodgkin/Reed–Sternberg (HRS) cells amid a background of non-neoplastic cell populations comprising T- and B-lymphocytes and other cell types.[1] HRS cells and their reactive neighbouring cells cross-talk via a complex of cytokine and cell contact dependent interactions; these probably include proliferative and anti-apoptotic signals favouring tumour cell survival and expansion.[2]

The Revised European American Lymphoma (REAL)/World Health Organization (WHO) lymphoma classification[3] divides HL into two major types: classical and nodular lymphocyte predominant HL (NLPHL) (table 1). Classical HL is further separated into four subtypes: nodular sclerosis (NS), mixed cellularity (MC), lymphocyte depletion (LD) and a newly defined entity known as ''lymphocyte rich classical'' (LRC) HL. NLP and classical HL are separated on the basis of morphological, immunophenotypic and clinical differences.[4] For example, HRS cells of NLPHL have different morphology, being referred to as lymphocytic and histiocytic (L&H) cells; they rarely express the classical HL markers CD15 or CD30, but regularly express B-cell antigens such as CD20 and CD19, which are usually absent in HRS cells of classical HL.[5]

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ORIGIN OF HRS CELLS

Early phenotypic studies suggested that HRS cells might be derived from macrophages, dendritic reticulum cells or granulocytes. However, the identification of clonally rearranged immunoglobulin (Ig) genes by PCR analysis of single HRS cells micromanipulated from HL tissues provided evidence not only of their malignant character but also of their origin from B cells.[6] Tumour cells of both HL types carry somatic *IGH* mutations in the variable (*V*) region, indicating that they originate from germinal centre or post-germinal centre B cells. However, only L&H cells of NLPHL demonstrate intraclonal *V* gene diversity due to ongoing mutation, suggesting that they originate from differentiating germinal centre B cells. In contrast, in 25% of classical HL, HRS cells carry non-functional ''crippling'' mutations in the IG_VH gene rearrangements, suggesting that HRS cells originate from pre-apoptotic germinal centre B cells that were rescued from apoptosis by transforming events[7] (fig 1).

The lack of expression of functional surface immunoglobulin (B-cell receptor; BCR) is the hallmark of classical HL, and while in some cases this is certainly due to non-functional or destructive rearrangements, other mechanisms can also account for the loss of functional BCR. For example, the loss of immunoglobulin-specific transcription factors, BOB-1, OCT2 and PU.1 in HRS cells has been reported.[8–11] It has also been shown that, in a minority of cases, HRS cells carry mutations in the octamer region of the immunoglobulin gene promoter, which can prevent binding of Ig-specific transcription factors.[12 13] Epigenetic silencing can also suppress Ig transcription in HRS cells.[14]

Microarray profiling has revealed the down-regulation in classical HL of B-cell lineage gene expression, including many components of BCR signalling.[15] *ID2*, which causes a global down-regulation of B-cell genes by directly interacting and negatively regulating B-cell specific transcription factors, such as E2A and PAX5, is strongly and uniformly expressed in HRS cells. Amplification or genomic gain of the *ID2* locus has been reported in 50% of patients with HL and may account for its over-expression in some cases.[16 17] Activation of *NOTCH1*, which is expressed by HRS cells, can also suppress the B-cell phenotype[18] and could contribute to the characteristic loss of B-cell identity. It has been suggested that the down-regulation of B-cell identity might allow HRS cells or their progenitors to escape the apoptosis that should occur in the absence of functional BCR, though there is no direct experimental evidence in support of this at present.[19]

Occasionally, HL tumours express T-cell antigens, including granzyme B and T-cell intracellular antigen (TIA)-1. In some cases this has been shown to represent aberrant expression of T-cell antigens by HRS cells that show evidence of *IGH* gene rearrangement and are thus assumed to be B cell in origin.[20] However, in the same study a single HL case showed expression of T-cell markers and

Table 1 Comparison of classical and nodular lymphocyte predominant Hodgkin lymphoma

REAL/WHO classification	Morphology/immunophenotype of HRS cells	EBV association	Ig status
Classical Hodgkin lymphoma Nodular sclerosis Mixed cellularity Lymphocyte depletion Lymphocyte-rich	Typical HRS cells which are CD15+, CD20−, CD30+, CD45−	Positive or negative	Lack BCR expression Destructive or non-functional *IGH* rearrangements or loss of Ig-specific transcription factors
Nodular lymphocyte-predominant Hodgkin lymphoma	Atypical ''popcorn'' cells which are CD15−, CD20+, CD30−, CD45+,	Negative	Express BCR Functional rearrangements of Ig genes Evidence of intraclonal diversity indicating ongoing somatic hypermutation

REAL/WHO, Revised European American Lymphoma (REAL)/World Health Organization; HRS, Hodgkin/Reed–Sternberg; EBV, Epstein–Barr virus; BCR, B-cell receptor.

also TCR gene rearrangements, indicating that at least a minority of HL tumours are genuinely of T-cell origin.

EBV AND HODGKIN LYMPHOMA

EBV is a ubiquitous human herpesvirus that infects over 90% of humans and persists for the lifetime of the person.[21] First evidence that EBV might be involved in the pathogenesis of HL was provided by the detection of raised antibody titres to EBV antigens in HL patients when compared with other lymphoma patients,[22] and furthermore, that these raised levels preceded the development of HL by several years.[23] With the advent of cloned viral probes and Southern blot hybridisation methods, EBV DNA was initially detected in 20–25% of HL.[24] In situ hybridisation provided the first demonstration of the existence of viral DNA in the HRS cells.[25 26] Subsequently, the demonstration of the abundant EBV-encoded RNAs (EBER1 and EBER2) in HRS cells provided a sensitive method for detecting latent infection in situ. This technique is now generally accepted as the ''gold standard'' for the detection of latent EBV infection in clinical samples[27] (fig 2).

In EBV-associated HL, viral genomes are found in monoclonal form, indicating that infection of the tumour cells occurred prior to their clonal expansion.[25] In the majority of cases, EBV persists throughout the course of HL and is also found in multiple sites of HL.[28]

Although most EBV infections in children are asymptomatic or cause non-specific symptoms, when primary infection is postponed until adolescence it can result in infectious mononucleosis (IM) in 50% of patients.[21] The relative risk of developing HL in individuals with a history of IM, relative to those with no prior history, was shown to range between 2.0 and 5.0.[29] It has recently been shown that the risk of EBV-positive HL is increased four-fold after IM, whereas the risk of EBV-negative HL is not increased.[30 31]

The possibility that EBV may contribute to the pathogenesis of HL early in the transformation of the progenitor cells but is subsequently lost (''hit and run''), prompted the search for evidence of defective rearranged EBV DNA in tumours that by conventional testing (eg by detection of the EBERs) are virus negative. Such defective rearranged viral DNA has been previously detected in some cases of virus-negative sporadic Burkitt lymphoma,[32] and could result in partial elimination of EBV episomes from infected cells through the expression of BZLF1. In support of this possibility, Gan *et al* amplified sequences that span abnormally juxtaposed BamH1W and Z fragments (which characterise defective heterogeneous EBV DNA) from 2/24 EBER-negative HL tumours in which the standard viral genome could not be detected.[33] However, others using fluorescence in situ hybridisation (FISH) found no evidence of integrated EBV genomes in EBV-negative HL.[34] Furthermore, using quantitative PCR assays that spanned the whole genome, no evidence of deletion of EBV genomes in EBV-positive HL, or retention of EBV genomes in EBV-negative HL tissues, was found.[35] Therefore, it seems unlikely that EBV contributes to the development of EBV-negative HL.

The rate of detection of EBV in HL depends on factors such as country of residence, histological subtype, sex, ethnicity and age. EBV-positive HL is less common in developed populations, with percentages of 20–50% for North American and European cases,[27 36–38] 57% for HL in China,[39] but much higher rates in underdeveloped countries.[40 41] The increased incidence of EBV-positive HL in underdeveloped countries could be due to the existence of an underlying immunosuppression similar to that observed for African Burkitt lymphoma in a malaria-infected population. This is supported by higher EBV-positive rates in HL from HIV-infected patients.[42] Alternatively, the timing of EBV infection (which is likely to occur earlier in developing countries) might also be important.

EBV is more commonly associated with the MC subtype and less frequently with the other subtypes.[43 44] Furthermore, it is now generally accepted that NLPHL is an EBV-negative disease.[45] HL in the older age groups and in children, especially boys under 10 years, has been shown to be more likely to be EBV-associated than HL in young adults.[46–48] This has led to the suggestion that HL consists of three disease entities: HL of childhood (EBV-positive, MC type); HL of young adults (EBV-negative, NS type); and HL of older adults (EBV-positive, MC type).[48] The higher proportion of EBV associated HL cases in older adults, is probably due to reduced immunosurveillance and increased viral reactivation occurring as a consequence of advancing years.[49] The infrequent association of EBV with HL in young adulthood prompted the suggestion that a second virus might be involved, although there is little direct evidence to support this at present.[50–52] EBV-positive rates are generally higher in males than in females. EBV-positive HL also affects more Asians and Hispanics than whites or blacks,[46] and in the UK is more common in South Asian children compared with non-South Asian children.[53]

TRANSFORMING EVENTS IMPLICATED IN HRS PATHOGENESIS

A number of cell signalling pathways are known to be aberrantly activated in HL. The PI3K/Akt pathway was recently shown to be constitutively activated in HL-derived cell lines and in HRS cells from primary tumour tissues, where it was shown to contribute to the survival of these cells.[54] The active phosphorylated form of ERK is also aberrantly expressed in cultured and primary HL cells; inhibition of the upstream MEK kinase inhibited the phosphorylation of ERK and the proliferation of HL cell lines.[55] Kube *et al* have demonstrated the constitutive activation of STAT3 in HRS cells.[56] STAT6 and STAT5a constitutive activation has also been reported.[57 58]

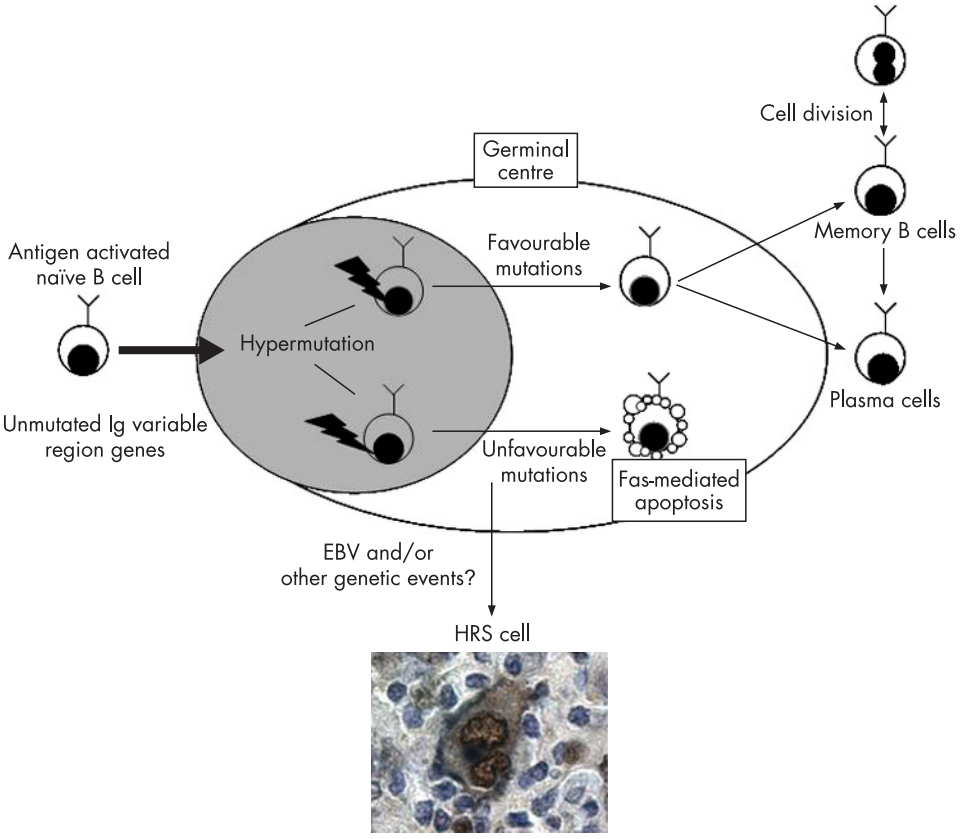

Figure 1 Hodgkin/Reed–Sternberg (HRS) cells may originate from pre-apoptotic germinal centre B cells. Naïve B cells are activated when they encounter cognate antigen. Activated B cells then migrate into B-cell follicles, proliferate and differentiate into centroblasts, thus establishing germinal centres. Germinal centre (GC) B cells undergo somatic hypermutation of the V region genes; cells with unfavourable mutations are eliminated by Fas-mediated apoptosis, whereas those carrying B-cell receptor (BCR) with high affinity for antigen will survive and leave the germinal centre as memory B cells or plasma cells. GC B cells carrying non-functional BCR should undergo apoptosis, but may be rescued by Epstein–Barr virus and/or still unknown genetic alterations. Such cells may be the progenitors of HRS cells.

Amplification of the *JAK2* locus is seen in some cases, providing a mechanistic explanation for the STAT activation.[59] Furthermore, HRS cells also have constitutively activated AP-1 with c-Jun and JunB overexpression.[60] AP-1 activation was also observed in anaplastic large cell lymphoma (ALCL), but not in other lymphoma types. Constitutive activation of NF-κB is a regular feature of HRS cells; inhibition of this pathway in HL cell lines leads to their increased sensitivity to apoptosis after growth factor withdrawal and impaired tumourigenicity in severe combined immunodeficiency (SCID) mice.[61 62]

Aberrant tyrosine kinase activity caused by various genetic alterations, such as activating point mutations, translocations or amplifications, frequently causes cellular transformation and has been observed in many different cancers. In mature B cells, several intracellular protein tyrosine kinases are essential for BCR signalling, whereas the expression of receptor tyrosine kinases (RTKs) is more limited; only expression of TRKA (tyrosine kinase receptor A) and MET have been described.[63–65] In contrast, HL cells display aberrant activation of several RTKs, including PDGFRA, EPHB1, RON, TRKB, and TRKA, in the absence of activating mutations.[66] Recently, it has been shown that aberrant tyrosine activity is more frequent in EBV-negative HRS cells, suggesting that RTK signalling might partially replace the effects of EBV in HL pathogenesis.[67]

Under normal circumstances HRS cell progenitors lacking a functional BCR should be eliminated by Fas (CD95)-mediated apoptosis in the germinal centre (GC). In vitro studies performed in our own laboratory and by others have demonstrated that HL-derived cell lines are resistant to Fas-mediated apoptosis.[68–71] It is well established that HRS cells express Fas,[70 72 73] and the rare occurrence of mutations in the *FAS* gene suggests that the general resistance of HRS cells to Fas-induced death is due to defects further downstream in the death receptor pathway.[74 75] c-FLIP is a proximal negative regulator of CD95-induced apoptosis that interferes with the formation of the death inducing signalling complex (DISC) required for death receptor induced death. A number of studies have shown that c-FLIP is highly expressed in HL-derived cell lines and primary HRS cells.[68 69 71 75] We showed that c-FLIP down-regulation was accompanied by the spontaneous death of HL cells, even in the absence of challenge with Fas agonistic antibody, CH11.[76] We also showed that HRS cells express Fas ligand (FasL); simultaneous knockdown of FasL and c-FLIP expression did not cause HRS cell death, demonstrating that endogenous FasL could initiate death receptor signalling when c-FLIP was silenced. Therefore, the down-regulation of c-FLIP unmasks a mechanism whereby HRS cells undergo self-induced Fas-mediated death. It should be noted that in a similar study, Mathas *et al* observed only a small increase in apoptosis following c-FLIP knockdown alone, but much greater cell death after the addition of either CH11 or TRAIL following c-FLIP knockdown.[69] Taken together, these data suggest that abrogation of c-FLIP expression might have therapeutic benefit in HL. HRS cells also have other defects in the apoptotic machinery. For example, they are defective in caspase 3-mediated apoptosis because of their high level expression of XIAP, an inhibitor of apoptosis that binds and inhibits the proteolytic activity of caspases-3, -7 and -9.[77]

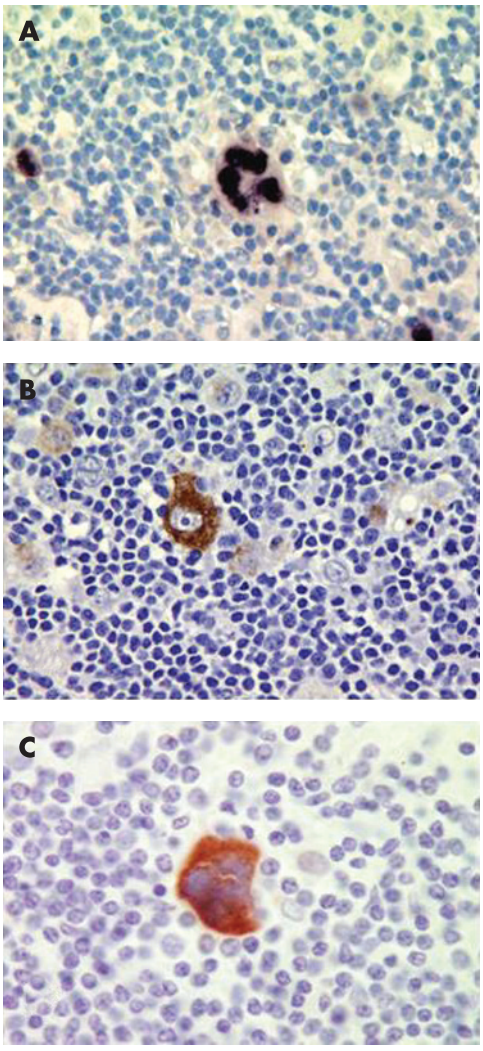

Figure 2 Gene expression in Epstein–Barr virus (EBV) associated Hodgkin lymphoma. (A) EBER expression (brown staining) in the nuclei of Hodgkin/Reed–Sternberg (HRS) cells. In situ hybridisation for EBER expression is the most reliable and sensitive method to detect the presence of latent EBV infection in clinical samples. (B) The latent membrane protein-1 (LMP1) and (C) LMP2 are both highly expressed in EBV-positive HRS cells. Not shown is the consistent expression of the EBV maintenance protein, EBNA1.

CONTRIBUTION OF EBV GENES TO THE PATHOGENESIS OF EBV-POSITIVE HODGKIN LYMPHOMA

EBV-positive HRS cells exhibit a type II form of virus latency, virus gene expression being limited to the EBERs, Epstein–Barr nuclear antigen-1 (EBNA1),[78] latent membrane protein 1 (LMP1),[43 44 79] LMP2,[79 80] (fig 2), and the Bam H1A rightward transcripts (BARTs).[79] EBV may contribute to the pathogenesis of HL before the HRS cell progenitor leaves the GC because it has been shown to rescue BCR-negative human tonsillar GC cells from apoptosis, and because HRS cells with crippling *IGH* mutations are almost exclusively found in EBV-positive patients.[81–85]

LMP1 induces many of the phenotypic changes observed in EBV-infected B cells, including expression of the B-cell activation markers, CD23 and CD40, interleukin (IL)-10 production and up-regulation of cell adhesion molecules such as ICAM1, LFA1 and LFA3. LMP1 also protects B cells from cell death by the up-regulation of several anti-apoptosis genes including *BCL2*, *MCL1* and *A20*.[86–89] LMP1 functions as a constitutively activated member of the tumour necrosis factor receptor (TNFR) superfamily activating cell signalling pathways in a ligand-independent manner. LMP1 can engage the MAP kinase cascade resulting in the activation of ERK, JNK and p38 and can stimulate the JAK/STAT pathway.[90–94] Two distinct functional domains referred to as C-terminal activation regions 1 and 2 (CTAR1 and CTAR2) have been identified on the basis of their ability to activate these signalling pathways. CTAR1 activates NF-κB mainly through the non-canonical pathway (TRAF3/NIK/IKK-alpha). In contrast, CTAR2 activates the canonical pathway by utilising TRAF6 and TAK1 to activate IKK-beta.[95] Although NF-κB activation can be induced by LMP1 in EBV-positive HRS cells, other routes to its activation must exist in EBV-negative cases. IκBα mutations have been reported in HL and might be more frequent in EBV-negative cases.[96–99] Amplification of the NF-κB/RelA locus at 2p13-16 is also frequent in HL.[100 101]

LMP1 can induce expression of DNA methyltransferases and mediate hypermethylation of the E-cadherin promoter in epithelial cells.[102 103] We have recently shown that LMP1 can up-regulate the Polycomb gene, *BMI1*, in HL cells.[104] Bmi-1 is a component of the polycomb repressive complex, PRC1; it is required for the initiation of gene silencing and induces lymphoid proliferation and the development of lymphomas in transgenic mice.[105] We showed that *BMI1* and LMP1 can regulate a shared subgroup of HL-associated genes, including the *ATM* tumour suppressor.[104] Therefore, it is likely that EBV mediates some its transforming effects through Bmi-1.

The identification that a virus strain carrying a 30 bp deletion in the LMP1 gene was more tumourigenic than the prototype B95.8 LMP1[106] led to numerous studies of the prevalence of this virus strain within EBV-associated cancers, including HL. In general, virus strains carrying this 30 bp deletion occur with a similar frequency in virus-positive tumour patients and in healthy donors from the same geographical region.[107] The exception to this is HL,[108] where some studies have shown an increased incidence of this deletion variant in HIV-positive HL compared to HIV-negative HL,[109] and in paediatric HL compared to normal controls.[110]

LMP2A is also highly expressed in EBV-positive HRS cells.[79] LMP2A was shown to compete for the binding of the Src and Syk protein tyrosine kinases, thereby blocking BCR signalling and induction of lytic cycle in B cells.[111] Paradoxically, expression of LMP2A in the B cells of transgenic mice abrogates normal B-cell development, allowing immunoglobulin-negative cells to colonise peripheral lymphoid organs,[112] suggesting that LMP2A can provide a BCR-like signal. LMP2A expression in transgenic mouse B cells down-regulates expression of many of the B-cell lineage genes that are absent or expressed at low levels in HRS cells (eg early B cell factor, PU.1, CD19, CD20).[113] In addition, LMP2A expression induces the up-regulation of genes involved in proliferation (eg MKI67, *PCNA*), protection from apoptosis (*BCLXL*, *BIRC5* (survivin)) and suppression of cell-mediated immunity (eg *IL13R*, EBI3).[113]

We recently showed that EBV infection of HL cells up-regulates autotaxin, a secreted tumour-associated factor with lysophospholipase-D activity. Up-regulation of autotaxin increased the generation of lysophosphatidic acid (LPA) and led to the enhanced growth and survival of Hodgkin lymphoma cells.[114] This is the first demonstration that virus infection leads directly to the synthesis of the growth-promoting lipid LPA and could represent a more general pathway utilised by herpesviruses during their normal life cycle or during the initiation and maintenance of virus-associated tumours. At this time it is unknown which EBV gene is responsible for this effect.

Studies of B cell subsets from healthy carriers have revealed that EBV persists in the peripheral blood in IgD-negative memory B cells (CD19+, CD23−, CD80/B7−) where viral protein expression may be restricted to LMP2A.[115] Following

primary infection of naïve or memory B cells, the virus expresses the EBNA2-dependent lymphoblastoid growth programme. The detection of both LMP1 and LMP2 in purified tonsillar memory B cells and germinal centre B cells[116] suggests that these viral proteins, through surrogate T-cell help (LMP1) and BCR engagement (LMP2A), provide the necessary signals for EBV-infected B cells to undergo antigen-independent proliferation in the germinal centre, in turn leading to replenishment of the pool of EBV-positive memory B cells. However, the recent demonstration that EBV-positive memory B cells are antigen selected suggests that these cells do not arise from a B-cell differentiation programme driven only by the virus. In this context LMP1 and LMP2 expression might favour the selection of EBV-infected B cells in the highly competitive antigen-dependent environment of the GC.[117] Together with as yet undefined cellular alterations, LMP1 and LMP2 could also favour the neoplastic transformation of GC B cells, leading to the development of EBV-positive HL.

Although this model is appealing, other studies suggest that the influence of LMP1 during B-cell differentiation is more complicated. LMP1 expression cannot be detected within GC of lymphoid tissues by immunohistochemistry[118] and has been shown to induce extra-follicular B-cell differentiation but not GC formation.[119] Therefore, it is possible that EBV accesses the memory-B-cell pool following an extra-follicular B-cell maturation programme which is driven by LMP1, and not through the conventional GC stage. CD40 can control the exit of B cells from the GC, and inhibit their further differentiation into plasma cells.[120] If LMP1 has similar effects on GC B-cell differentiation, an LMP1-expressing post-GC/pre-plasma cell may emerge from which the HRS cell develops. This would be consistent with the finding that HRS cells often express some of the markers of plasma cell differentiation; and also with the observation that the completion of plasma cell differentiation may be prejudicial to the maintenance of viral latency because it can result in the reactivation of viral replication.[121]

FAILURE OF THE IMMUNE RESPONSE TO ELIMINATE EBV-INFECTED HRS CELLS AND ATTEMPTS TO DEVELOP IMMUNOTHERAPEUTIC STRATEGIES

LMP2A and LMP1 are targets for cytotoxic T lymphocytes (CTLs) in association with different MHC class I restriction elements in vitro.[122 123] In vitro HL cells can process and present epitopes from LMP1 and LMP2A in the context of multiple class I alleles and are sensitive to lysis by EBV-specific CTLs.[131 132] However, EBV-infected HRS cells survive in vivo. HRS cells express the thymus and activated regulated chemokine (TARC), IL-10, IL-13 and TGFβ which could counteract EBV-specific CTL responses.[124–127] Surprisingly, EBV-positive cases of HL have been shown to contain more activated CTLs and express higher levels of MHC class I than EBV-negative cases.[128–131]

EBV-specific CTLs can be generated from patients with advanced HL, albeit at lower frequency than normal controls.[133] These EBV-specific CTLs survived and had antiviral activity in vivo; however, despite the resolution of some symptoms and the stabilisation of disease, all HL patients failed to recover from their disease. Successful CTL therapy for EBV-positive HL will require not only EBV-specific CTL with improved cytotoxicity, but probably also modification of the tumour microenvironment to remove the inhibitory barriers which inhibit CTL function. Antigen presentation systems may improve the cytolytic activity of CTLs. For example, exposure to AdE1-LMPpoly (a replication-deficient adenoviral system which encodes a glycine alanine repeat-deleted EBNA1 covalently linked to multiple $CD8^+$ T cell epitopes from LMP1 and LMP2) was effective in expanding T cells specific for LMP1, LMP2A, and EBNA1, across a range of HLA types.[134] A recombinant poxvirus vaccine encoding a polypeptide protein comprising six HLA A2 restricted epitopes derived from LMP1 (''LMP1 polyepitope vaccine''), can generate stronger anti-LMP1 responses.[136] CTLs generated by exposure to LMP2A-expressing dendritic cells demonstrate increased cytotoxicity.[135]

There are a number of possibilities to alleviate the CTL inhibitory effect of the microenvironment,[137 138] but the depletion of regulatory T cells (Tregs) is likely to be of prime importance. Recent studies show that both tumour infiltrating lymphocytes and peripheral blood mononuclear cells from HL patients contain many Tregs.[139] A recent study showed that Tregs which express LAG-3 are more frequent in EBV-positive compared with EBV-negative HL.[139] Furthermore, the level of LAG-3 expression on the tumour-infiltrating lymphocytes was coincident with impairment of T-cell activity against LMP1 and LMP2, whereas deletion of CD4+ LAG-3+ T-cells enhanced LMP-specific immunity.

Take-home messages

- Epstein-Barr virus (EBV) is associated with only a proportion of cases of Hodgkin lymphoma (HL), where the virus is present in the tumour cell populations. The virus-negative and virus-positive forms of the disease are morphologically similar but appear to differ in terms of their precise underlying molecular changes.
- EBV contributes to the aberrant activation of key signalling pathways in HL; understanding how EBV subverts cellular physiology can also inform our understanding of EBV-negative HL.
- The development of EBV-associated HL may be regarded as an unintentional consequence of the normal viral life cycle which is designed to enable EBV to persist in the B cell pool of normal carriers.
- Understanding the mechanisms by which EBV transforms cells and escapes the immune system will be important for the development of strategies to treat patients with EBV-associated malignancies.

SUMMARY

A proportion of HL tissues harbour EBV within tumour cells. Superficially at least, there are surprisingly few differences between EBV-positive and EBV-negative HRS cells. Emerging evidence suggests that while EBV is able to subvert cellular processes in favour of growth and survival, cellular genetic events are required to do this when EBV is absent. The challenge is to unravel this complexity by detailed consideration of the function of latent EBV genes in the appropriate cellular context. It is hoped that this approach will reveal more fundamental aspects of HL pathogenesis and pave the way for more targeted therapies for HL patients.

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