UNIVERSITY OF BIRMINGHAM
University of Birmingham Research at Birmingham

Contribution of EpsteinBarr Virus Latent Proteins to the Pathogenesis of Classical Hodgkin Lymphoma

Vrzalikova, Katerina; Sunmonu, Taofik; Reynolds, Gary; Murray, Paul

DOI:
10.3390/pathogens7030059

License:
Creative Commons: Attribution (CC BY)

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Vrzalikova, K, Sunmonu, T, Reynolds, G & Murray, P 2018, 'Contribution of EpsteinBarr Virus Latent Proteins to the Pathogenesis of Classical Hodgkin Lymphoma', *Pathogens*, vol. 7, no. 3, 59.
https://doi.org/10.3390/pathogens7030059

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
Vrzalikova, K.; Sunmonu, T.; Reynolds, G.; Murray, P.Contribution of Epstein–Barr Virus Latent Proteins to the Pathogenesis of Classical Hodgkin Lymphoma. Pathogens 2018, 7, 59.
https://doi.org/10.3390/pathogens7030059

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.
•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
•Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 24. Apr. 2024

pathogens

MDPI

Review

Contribution of Epstein–Barr Virus Latent Proteins to the Pathogenesis of Classical Hodgkin Lymphoma

Katerina Vrzalikova [1,*], Taofik Sunmonu [1], Gary Reynolds [2] and Paul Murray [1,3,*]

[1] Institute for Cancer and Genomic Medicine, University of Birmingham, Birmingham B15 2TT, UK; taosun77@gmail.com
[2] Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham B15 2TT, UK; g.m.reynolds@bham.ac.uk
[3] Department of Clinical and Molecular Pathology, Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University, 775 15 Olomouc, Czech Republic
* Correspondence: k.vrzalikova@bham.ac.uk (K.V.); p.g.murray@bham.ac.uk (P.M.); Tel.: +44-121-414-4021 (P.M.)

Received: 8 May 2018; Accepted: 20 June 2018; Published: 27 June 2018

Abstract: Pathogenic viruses have evolved to manipulate the host cell utilising a variety of strategies including expression of viral proteins to hijack or mimic the activity of cellular functions. DNA tumour viruses often establish latent infection in which no new virions are produced, characterized by the expression of a restricted repertoire of so-called latent viral genes. These latent genes serve to remodel cellular functions to ensure survival of the virus within host cells, often for the lifetime of the infected individual. However, under certain circumstances, virus infection may contribute to transformation of the host cell; this event is not a usual outcome of infection. Here, we review how the Epstein–Barr virus (EBV), the prototypic oncogenic human virus, modulates host cell functions, with a focus on the role of the EBV latent genes in classical Hodgkin lymphoma.

Keywords: Epstein–Barr virus; Hodgkin lymphoma; latency; B cells

1. EBV Is a Transforming B Lymphotropic Virus

EBV is a gamma-herpesvirus that persists asymptomatically in the majority of the world's adult population through its ability to colonise the B-cell system. Primary infection is usually asymptomatic, in most cases occurring early in life; only a few individuals develop symptoms if infection occurs later, resulting in infectious mononucleosis (IM).

EBV-infected B cells present in the blood of asymptomatically infected individuals when cultured can grow out as EBV-transformed cell lines, these are referred to as lymphoblastoid cell lines (LCL). This can happen only if T cells are removed or inhibited, for example with cyclosporin A, underscoring the requirement for control over the virus by T cells in people [1]. LCL can be made by infecting B cells with EBV in vitro. The EBV genes required for transformation of B cells include 'latent' genes, that is, those present in latency, when no virions are made. Another phase of infection can occur when the virus undergoes the replicative cycle in which new virions are assembled and released; the so-called 'lytic' genes are required for this process. The latent genes encode six Epstein–Barr nuclear antigens (EBNAs 1, 2, 3A, 3B, 3C and EBNA-LP), the latent membrane proteins (LMP1, LMP2A and LMP2B), two noncoding Epstein–Barr-encoded RNAs (EBER1 and EBER2), and viral miRNA [2,3]. LCL express all known EBV latent genes; this form of infection is known as latency III. Only EBNA2, EBNA3A, EBNA3C and LMP1 have been shown to be essential for the in-vitro transformation of B cells [4], although EBNA-LP was recently shown to be required for the transformation of naïve B cells [5].

2. Asymptomatic Infection of B Cells

EBV is a persistent virus, residing in memory B cells for the life of the infected host [6]. There are several models to explain this. In the so-called germinal centre (GC) model, EBV infection of naïve B cells initiates their expansion through proliferation, the resulting immortalized cells expressing the latency III programme. At some point these EBV-infected B cells acquire a GC phenotype, although it is not certain if this occurs in the context of a GC structure. Here the cells express latency II, an alternative form of latency, characterised by expression of EBNA1, LMP1 and LMP2 (of which there are two isoforms; A and B). However, unlike latency III, the other EBNAs are not expressed [7]. LMP1 and LMP2A are CD40 and B-cell receptor (BCR) mimics, respectively; together they are responsible for providing the necessary cues for the post-GC differentiation of the EBV-infected cells [8,9]. The function of LMP2B is poorly understood but it may play a role in negatively regulating LMP2A's function [10]. After differentiation to memory B cells, the virus expresses no viral proteins; this is known as latency 0 and occurs to prevent detection of the infected cell by the host's immune response. There is only occasional EBNA1 expression which is required by the virus to ensure episome segregation when the B cells proliferate (this phase is known as latency I) [7]. Alternatively, the virus-infected B cell can differentiate into a plasma cell; this process switches on the virus replicative cycle and provides the means for the virus to make new virions, which can be shed into the oral cavity from trafficking plasma cells in the oral lymphoid tissues [11].

B-cell lymphomas, including Hodgkin lymphoma (HL), Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL), can result when these finely tuned interactions between the virus and the host B cell go wrong. EBV-associated HL is the focus of this review.

3. Hodgkin Lymphoma (HL)

The hallmark of HL is the existence of a tumour microenvironment (TME) rich in nonmalignant T- and B-lymphocytes and other cell types which surround a minor population of malignant Hodgkin/Reed–Sternberg (HRS) cells. There is evidence that crosstalk between HRS cells and these nonmalignant cells of the TME provides essential signals to HRS cells for their growth and survival. As we shall see later, these TME interactions also promote the escape of HRS cells from an EBV-specific immune response [12].

HL is divided into two major types; classical HL (cHL) and nodular lymphocyte predominant HL (NLPHL). cHL is further separated into four subtypes; nodular sclerosis, mixed cellularity, lymphocyte depletion and lymphocyte-rich classical HL. NLPHL and cHL are morphologically and immunophenotypically distinct; the tumour cells of NLPHL, known as lymphocytic and histiocytic (L&H) cells, are often negative for classical HL markers (e.g., CD15, CD30), but express B-cell markers, including CD20 and CD19, which are absent from the HRS cells of cHL [13].

3.1. B-Cell Origin of Hodgkin Lymphoma

The tumour cells of HL have clonally rearranged immunoglobulin genes and somatic IGH mutations in the variable (V) region, indicating their GC or post-GC origin [14–16]. However, there is one major difference between cHL and NLPHL in this respect; while the L&H cells of NLPHL show intraclonal V gene diversity indicating that they are derived from differentiating GC B cells [15,17], around one quarter of cHL contain HRS cells bearing nonfunctional mutations in the IGVH genes. Cells bearing these damaging mutations should die by apoptosis (because the rescue of B cells from apoptosis in the GC requires a functional B-cell receptor). For this reason, transforming events occurring in cHL must include the rescue of progenitors from apoptosis [14–16].

As indicated above, the HRS cells of cHL do not express typical B-cell markers. In fact, there is global downregulation of B-cell lineage markers accompanied by the overexpression of markers of other haematopoietic cell types including T cells, NK cells and myeloid cells [18–23]. The loss of B-cell identity results in part from the disruption of networks of transcription factors including

PAX5, early B-cell factor 1 (EBF1) and TCF3/E2A that regulate normal B-cell development and differentiation [22–35].

3.2. Deregulated Cellular Signalling in Classical Hodgkin Lymphoma

HRS cells show constitutive activation of canonical and noncanonical nuclear factor kappa B (NF-κB) signalling [24]. Expression of different TNF receptors, such as CD30, CD40, TACI, BCMA and RANK, can induce NF-κB activation in HRS cells [25–28], following ligation by factors present in the TME [29,30]. IRF5 is also aberrantly activated in HRS cells and co-operates with NF-κB [31]. Notch signalling can also induce NF-κB activation [32].

Activation of the NF-κB pathway can also result from genomic alterations, including c-REL amplifications [33–36], mutations in IκB inhibitors [37–41], overexpression of BCL3 [42,43] and mutations/deletions in TNFAIP3/A20 [36,44,45]. The noncanonical NF-κB pathway also contributes to the survival of HL cell lines through the stabilisation of the NF-κB inducing kinase (NIK) protein [46]. Chromosomal gains of NIK are reported in primary cHL [36,46,47].

HRS cells can secrete different cytokines, including IL-3, IL-7, IL-9 and IL-13 [48–52], and IL-21 [53,54], which activate JAK/STAT signalling [54–57]. JAK/STAT signalling can also be dysregulated through JAK2 amplification or loss-of-function mutations of SOCS1 and PTPN1/PTPB1 [58–62].

HRS cells also show deregulated AP-1 signalling [63,64], and we and others have shown that phosphatidylinositide-3-kinase (PI3-K) signalling is constitutively activated in cHL [65,66]. Recently, we have shown that a feed-forward signalling loop driven by the sphingosine-1-phosphate (S1P) receptor-1 (S1PR1) is responsible, at least in part, for the aberrant activation of PI3-K signalling in cHL [67]. Aberrant overexpression and/or activation of different receptor tyrosine kinases (RTK) is also a feature of HRS cells. Two collagen-binding RTK, DDR1 and DDR2, are of particular interest given that many cases of cHL show prominent collagen deposition [68–70]. We have shown that the activation of DDR1 by collagen is important for the survival of HRS cells [71].

3.3. EBV Is Involved in the Pathogenesis of a Subset of Classical Hodgkin Lymphoma

Elevated antibody titres to the EBV viral capsid antigen (VCA) were initially observed in the blood of cHL patients [72], and appear in people several years prior to the development of cHL [73]. A significantly increased risk of EBV-positive, but not of EBV-negative, cHL is reported for individuals who have had IM [74–77]. In 1985, the anticomplement immunofluorescence assay was used to detect an EBV protein in HRS cell nuclei; later this protein was designated EBNA1 [78]. Subsequently, EBV DNA was detected in around one-quarter of whole HL biopsies by Southern blot [79]. Later, EBV genomic DNA and EBER expression were detected in HRS cells using sensitive in-situ hybridisation assays [80–82]. EBV has also been shown to be present in HRS cells throughout the course of disease and in multiple sites of disease [83]. As with many other EBV-associated cancers, viral genomes in HRS cells exist in monoclonal form; thus it is very likely that all EBV-infected tumour cells arose from a single infected progenitor [80]. It must be noted that there are those who still maintain that EBV is simply a passenger in the process of lymphomagenesis. However, were this the case then the frequency of EBV-positive lymphomas in the population would approximate the frequency of EBV-infected B cells in individuals, that is, 1 in 10^6, and not the 1 in 3 observed for cHL in the West (see below).

EBV rates in cHL vary depending upon age, gender, histological subtype, ethnicity and country of residence [84,85]. EBV is more commonly found in the tumour cells of cHL patients from underdeveloped countries, and less frequently in cHL patients from the West [86,87]. In Europe and North America, EBV rates in cHL are higher in older people and in children <10 years old, but much lower in young adults [88,89], but also vary by ethnicity and social class [84,90]. These data have been used to suggest that cHL actually comprises three different diseases: (1) childhood cHL, which is EBV-positive and often of mixed cellularity type; (2) young-adult cHL (EBV-negative, nodular sclerosis type); and (3) cHL of older adults (EBV-positive, and usually of mixed cellularity type) [88]. It is

entirely likely that EBV's role in disease pathogenesis differs within these age groups. Furthermore, there is almost certainly a contribution from disorders of EBV-specific immune function. For example, the higher rates of EBV-positive cHL in the elderly have been attributed to declining EBV-specific immunity associated with advancing age [88].

3.4. Contribution of EBV Latent Genes to the Pathogenesis of Classical Hodgkin Lymphoma

The EBV genome in HRS cells expresses a latency II pattern including EBNA1 and the latent membrane proteins as well as the viral RNA (Epstein–Barr-encoded RNAs, EBER1 and EBER2, and BART miRNAs). The contribution of virally encoded RNA to the pathogenesis of EBV-associated cHL remains very poorly understood. We now provide a description of the role of EBNA1, LMP1 and LMP2A in the pathogenesis of cHL (Figure 1).

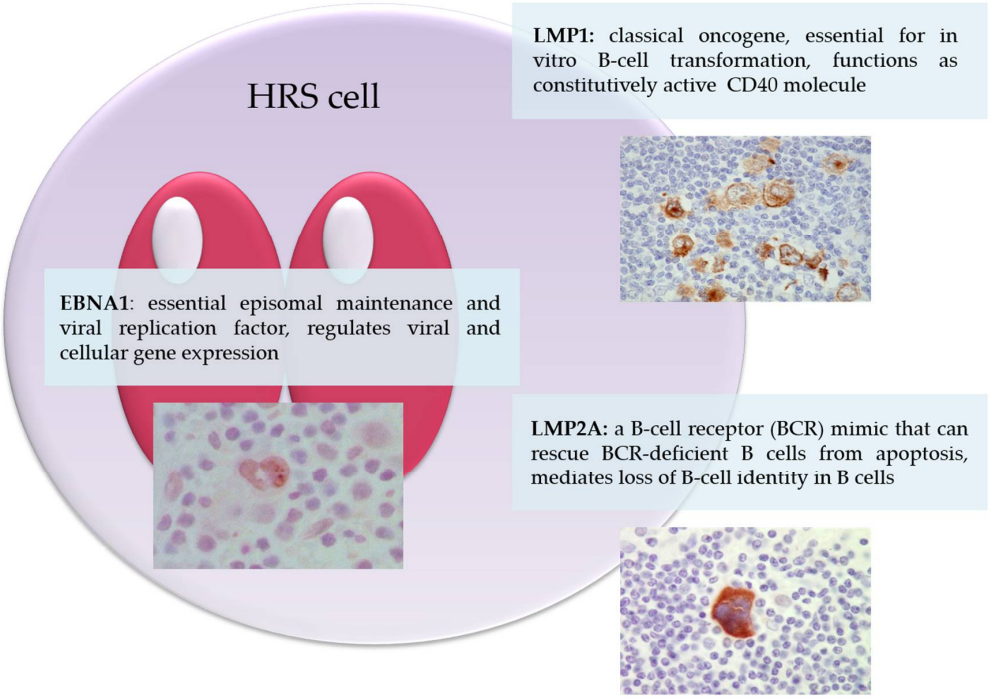

Figure 1. Epstein–Barr virus latent proteins expressed in Hodgkin/Reed–Sternberg cells. Depicted is a Hodgkin/Reed–Sternberg cell with indicated functions of the viral EBNA1, LMP1 and LMP2A proteins.

3.4.1. Epstein–Barr Virus Nuclear Antigen-1 (EBNA1)

The maintenance of EBV episomes in infected cells requires EBNA1 which acts both as a viral replication factor and as a tether binding the viral genome to the chromosomes and ensuring faithful segregation of episomes during mitosis [91].

EBNA1 is also reported as a regulator of the transcription of both viral and cellular genes [92–94]. Several studies suggest that EBNA1 can directly influence the growth and survival of B cells. For example, knock-down of EBNA1 reduced the survival of BL cells carrying viral episomes but did not cause loss of virus genomes, and also reduced the survival of Namalwa cells, which carry EBV as an integrated genome [95]. EBNA1 also inhibited p53-mediated apoptosis in response to UV irradiation, whereas mutant EBNA1 offered no such protection [95,96]. EBNA1 also enhances the formation of cHL xenografts in NOD-SCID mice [97]. EBNA1 can inhibit TGFβ signalling, in part through increasing the turnover of SMAD2 [98,99], and can promote the growth and survival of cHL cells by downregulating the TGFβ target gene, PTPRK [98]. EBNA1 was also shown to upregulate expression of the chemokine CCL20 in HRS cells, which in turn promoted the migration of regulatory

T cells [100]. Thus, EBNA1 might contribute to immune evasion of EBV-infected HRS cells. EBNA1 can also induce B-cell lymphomas in transgenic mice [101,102], although these results were not reproduced in another independent transgenic mouse study [103].

EBNA1 could mediate some of its effects on cellular transcription through its bipartite Gly–Arg-rich domain which resembles the AT-hook of High Mobility Group A architectural transcription factors. This domain of EBNA1 mediates an interaction with cellular chromatin causing increased mobility of histone H1 [104]. EBNA1 also interacts with numerous sequence-specific host chromosome sites through its C-terminal DNA-binding domain [105,106]. Recently, it was shown that multiple EBNA1 binding sites are located proximal to transcription start sites in the human genome [107,108]. In one of these studies, EBNA1 depletion from LCL reduced their proliferation and led to the loss of expression of cellular genes that were also shown to bind EBNA1 in ChIPseq experiments [108]. These included MEF2B, EBF1 and IL6R, which, when depleted, partially phenocopied EBNA1 depletion by decreasing the cell growth and viability of latently infected cells [108]. Thus, EBNA1 is apparently capable of regulating key survival genes in B cells. Because of the potential critical role of EBNA1 in maintaining virus infection and also potentially in driving oncogenesis, there is emerging interest in targeting EBNA1 therapeutically (Figure 2).

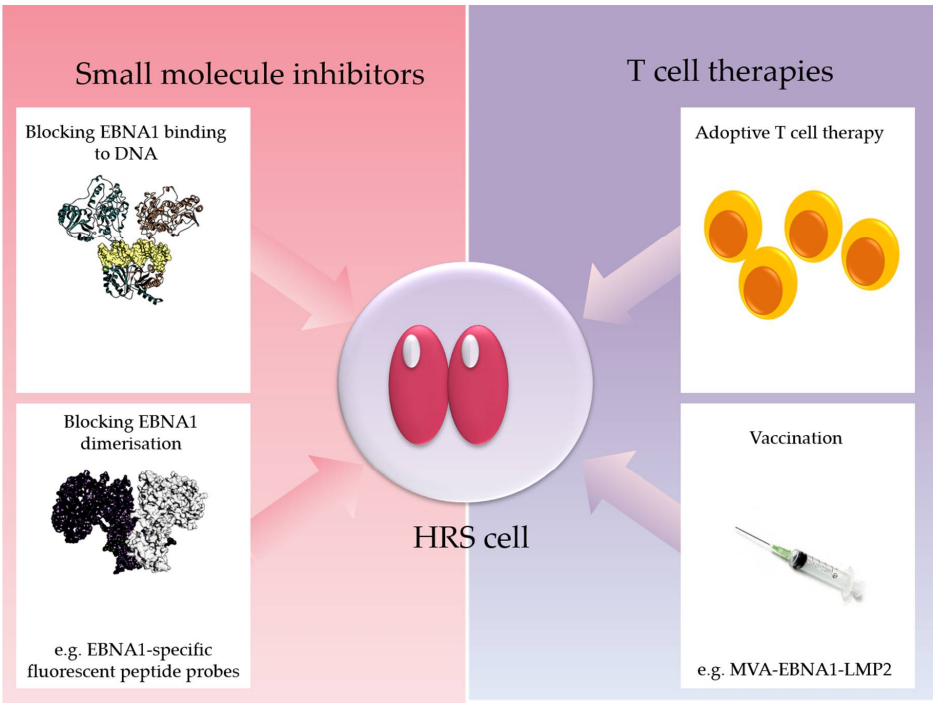

Figure 2. EBNA1 is an emerging target for therapeutic intervention. Shown is an HRS cell expressing EBNA1. Possibilities to target EBNA1 therapeutically are indicated and include the use of small-molecule inhibitors of EBNA1, for example using drugs that block EBNA1 binding to DNA and EBNA1-specific fluorescent peptide probes which prevent EBNA1 dimerization [109–111], therapeutic EBV vaccines including MVA-EBNA1-LMP2 containing an EBNA1-LMP2 fusion protein [112], and adoptive T-cell therapies [113,114]. Other approaches include relieving Gar-mediated suppression of EBNA1 translation which can potentially boost EBNA1 recognition by T cells (e.g., PhenDC3) [115].

3.4.2. Latent Membrane Protein-1 (LMP1)

LMP1 has many functional similarities to a constitutively activated CD40 receptor [8,116–120], and is able to induce cell signalling pathways relevant to HL pathogenesis including the NF-κB, JAK/STAT, AP-1 and phosphatidylinositol-3 kinase (PI3K)/AKT pathways described earlier [120–124]. In fact, LMP1 could provide the signal for the activation of these pathways in the absence of mutations.

This is well illustrated in the case of the TNFAIP3 gene which encodes a protein that is a negative regulator of NF-κB, and is almost always mutated only in EBV-negative cHL [125,126].

Because it regulates multiple signalling pathways, LMP1 is a major EBV regulator of cellular transcription. LMP1 can modify cellular transcription through a multitude of mechanisms that include the overexpression of the transcription factor ID2 [127], through DNA methyltransferases and protein arginine methyltransferases [128–130], by modification of the H3K27me3 histone mark, or alternatively by changing the levels of cellular miRNAs [131–136]. c-FLIP, which negatively regulates Fas-induced apoptosis, is also induced by LMP1, and this way could contribute to the rescue of BCR-negative GC B-cell progenitor from apoptosis [137,138]. LMP1 also downregulates expression of the telomeric repeat binding factors, TRF1, TRF2 and protection of telomeres (POT)-1 [139,140]. This leads to 3D shelterin disruption, resulting in telomere dysfunction, development of complex chromosomal rearrangements, and the generation of multinucleated HRS-like cells. LMP1 can also inhibit the differentiation of EBV-infected B cells to the plasma cell stages by inhibiting the expression of BLIMP1α, potentially contributing to a block in differentiation at the HRS-like stage [141].

LMP1 probably also contributes to the formation of the cHL TME because it has been shown to induce secretion of multiple chemoattractants in EBV-infected HRS cells [142–144]. While the cHL TME can support HRS cell growth and survival, it also helps the tumour cells escape EBV-specific immunity, including CD4+ and/or CD8+ T cells which can recognise epitopes from the viral latent proteins expressed in HRS cells [145–155].

A major immune evasion mechanism in cHL involves the overexpression of the programmed death ligands, PD-L1 and PD-L2, which are encoded by the CD274 and PDCD1LG2 genes, respectively. PD-L1 is overexpressed by tumour cells and macrophages in both EBV-positive and EBV-negative cHL, and in EBV-associated DLBCL [156]. In contrast, neither the malignant nor the nonmalignant cells of NLPHL, DLBCL NOS (not otherwise specified), or BL, express PD-L1 [156]. LMP1 can induce PD-L1 expression [157]. Amplification of PD-L1 and PD-L2 or reciprocal translocation involving CIITA also contribute to their overexpression in cHL [158]. Co-expression of PD-1 and PD-L1 is associated with poor prognosis in cHL [159].

Virus gene expression in HRS cells can also be modified by the interaction of EBV-infected tumour cells with the cHL TME. This is well illustrated in the case of LMP1, the expression of which can be stimulated by exposure of HRS cells to cytokines such as IL-4, IL-10, IL-13 and IL-21 [143,160,161]. The cHL TME can also potentially influence the outcome of virus gene expression. As described above, the collagen receptor DDR1 is overexpressed in cHL and we have shown that this effect is the result of its upregulation by LMP1 [71]. Thus, LMP1 can promote DDR1 activation and the survival of HRS cells, but only when collagen is present in the cHL TME [71].

3.4.3. Latent Membrane Protein-2 (LMP2)

There are two LMP2 isoforms, LMP2A and LMP2B. They differ insofar as the 5′ exon of LMP2B is noncoding. LMP2A functions as a BCR mimic, allowing B-cell development in the absence of normal BCR signalling [9,162]. LMP2A activates cellular signalling required for B-cell survival, including the RAS/PI3K/AKT pathway [163]. EBV can immortalise BCR-negative GC B cells in vitro [164–166] and LMP2A is essential for this [167]. LMP2A can induce entry to the EBV lytic cycle in the absence of a functional BCR, but cannot do so when downstream BCR components are missing, as is the case in cHL [168]. LMP2A suppresses B-cell lineage gene expression, and is thus able to recapitulate some aspects of aberrant gene expression observed in HRS cells [168–171]. LMP2A constitutively activates Notch1 signalling which contributes to the loss of B-cell identity through altered transcription of E2A and EBF [172].

3.4.4. Potential Interactions between LMP1 and LMP2A in B-Cell Lymphomagenesis

In transgenic mice, LMP2A expression induces autoimmunity [173], whereas LMP1 expression leads to B cell lymphoma [174,175]. However, the expression of both LMP1 and LMP2A in the same

mouse B cells results in no significant B-cell abnormalities [176], suggesting that LMP2A may be a tumour suppressor. Recently, it was shown that LMP1 was dispensable for EBV-induced lymphoma formation in cord blood-humanized mice and that deletion of LMP2A delayed the onset of lymphoma in this model [177]. In another study, a mouse model was generated with conditional GC B-cell co-expression of LMP1 and LMP2A. There was little impact of LMP1 and LMP2A co-expression on the phenotype of B cells in immunocompetent mice [178]. However, when NK and T cells were depleted, there was extensive outgrowth of plasmablasts, characterised by overexpression of many markers known to be overexpressed in HRS cells, including CD30 [178].

4. Conclusions

EBV is associated with a variable subset of HL. Despite an increasing knowledge of the pathogenesis of these tumours, it is perhaps surprising that there are currently no standard-of-care therapies that target the virus or the molecular abnormalities specific to EBV-positive tumours. However, EBV-targeted therapies are in clinical development and in the near future could well be added to the increasing armory of drugs already available to HL patients. They include small-molecule inhibitors of EBNA1, which have been shown to be effective against EBV-infected cells in preclinical models, as well as adoptive T-cell therapy and therapeutic vaccination. These latter approaches could be envisaged to be particularly effective when used in combination with existing immune checkpoint therapies.

Author Contributions: K.V., T.S., G.R. and P.M. wrote the manuscript.

Funding: This work was supported by Bloodwise (K.V., P.M.) and in part by grants RVO: 61989592 and NPS I LO1304 from the Czech Ministry of Education (P.M.).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Rickinson, A.B.; Rowe, M.; Hart, I.J.; Yao, Q.Y.; Henderson, L.E.; Rabin, H.; Epstein, M.A. T-cell-mediated regression of "spontaneous" and of epstein-barr virus-induced b-cell transformation in vitro: Studies with cyclosporin a. *Cell. Immunol.* **1984**, *87*, 646–658. [CrossRef]
2. Kerr, B.M.; Lear, A.L.; Rowe, M.; Croom-Carter, D.; Young, L.S.; Rookes, S.M.; Gallimore, P.H.; Rickinson, A.B. Three transcriptionally distinct forms of epstein-barr virus latency in somatic cell hybrids: Cell phenotype dependence of virus promoter usage. *Virology* **1992**, *187*, 189–201. [CrossRef]
3. Pfeffer, S.; Zavolan, M.; Grasser, F.A.; Chien, M.; Russo, J.J.; Ju, J.; John, B.; Enright, A.J.; Marks, D.; Sander, C.; et al. Identification of virus-encoded microrna. *Science* **2004**, *304*, 734–736. [CrossRef] [PubMed]
4. Young, L.S.; Yap, L.F.; Murray, P.G. Epstein-barr virus: More than 50 years old and still providing surprises. *Nat. Rev. Cancer* **2016**, *16*, 789–802. [CrossRef] [PubMed]
5. Szymula, A.; Palermo, R.D.; Bayoumy, A.; Groves, I.J.; Ba Abdullah, M.; Holder, B.; White, R.E. Epstein-barr virus nuclear antigen ebna-lp is essential for transforming naive b cells, and facilitates recruitment of transcription factors to the viral genome. *PLoS Pathog.* **2018**, *14*, e1006890. [CrossRef] [PubMed]
6. Babcock, G.J.; Decker, L.L.; Volk, M.; Thorley-Lawson, D.A. Ebv persistence in memory b cells in vivo. *Immunity* **1998**, *9*, 395–404. [CrossRef]
7. Babcock, G.J.; Hochberg, D.; Thorley-Lawson, D.A. The expression pattern of epstein-barr virus latent genes in vivo is dependent upon the differentiation stage of the infected b cell. *Immunity* **2000**, *13*, 497–506. [CrossRef]
8. Gires, O.; Zimber-Strobl, U.; Gonnella, R.; Ueffing, M.; Marschall, G.; Zeidler, R.; Pich, D.; Hammerschmidt, W. Latent membrane protein 1 of epstein-barr virus mimics a constitutively active receptor molecule. *EMBO J.* **1997**, *16*, 6131–6140. [CrossRef] [PubMed]
9. Caldwell, R.G.; Wilson, J.B.; Anderson, S.J.; Longnecker, R. Epstein-barr virus lmp2a drives b cell development and survival in the absence of normal b cell receptor signals. *Immunity* **1998**, *9*, 405–411. [CrossRef]

10. Rovedo, M.; Longnecker, R. Epstein-barr virus latent membrane protein 2b (lmp2b) modulates lmp2a activity. *J. Virol.* **2007**, *81*, 84–94. [CrossRef] [PubMed]
11. Laichalk, L.L.; Thorley-Lawson, D.A. Terminal differentiation into plasma cells initiates the replicative cycle of epstein-barr virus in vivo. *J. Virol.* **2004**, *79*, 1296–1307. [CrossRef] [PubMed]
12. Liu, Y.; Sattarzadeh, A.; Diepstra, A.; Visser, L.; van den Berg, A. The microenvironment in classical hodgkin lymphoma: An actively shaped and essential tumor component. *Semin. Cancer Biol.* **2014**, *24*, 15–22. [CrossRef] [PubMed]
13. Anagnostopoulos, I.; Hansmann, M.L.; Franssila, K.; Harris, M.; Harris, N.L.; Jaffe, E.S.; Han, J.; van Krieken, J.M.; Poppema, S.; Marafioti, T.; et al. European task force on lymphoma project on lymphocyte predominance hodgkin disease: Histologic and immunohistologic analysis of submitted cases reveals 2 types of hodgkin disease with a nodular growth pattern and abundant lymphocytes. *Blood* **2000**, *96*, 1889–1899. [PubMed]
14. Kuppers, R.; Rajewsky, K. The origin of hodgkin and reed/sternberg cells in hodgkin's disease. *Annu. Rev. Immunol.* **1998**, *16*, 471–493. [CrossRef] [PubMed]
15. Kuppers, R.; Rajewsky, K.; Zhao, M.; Simons, G.; Laumann, R.; Fischer, R.; Hansmann, M.L. Hodgkin disease: Hodgkin and reed-sternberg cells picked from histological sections show clonal immunoglobulin gene rearrangements and appear to be derived from b cells at various stages of development. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 10962–10966. [CrossRef] [PubMed]
16. Kuppers, R.; Rajewsky, K.; Zhao, M.; Simons, G.; Laumann, R.; Fischer, R.; Hansmann, M.L. Hodgkin's disease: Clonal ig gene rearrangements in hodgkin and reed-sternberg cells picked from histological sections. *Ann. N. Y. Acad. Sci.* **1995**, *764*, 523–524. [CrossRef] [PubMed]
17. Marafioti, T.; Hummel, M.; Anagnostopoulos, I.; Foss, H.D.; Falini, B.; Delsol, G.; Isaacson, P.G.; Pileri, S.; Stein, H. Origin of nodular lymphocyte-predominant hodgkin's disease from a clonal expansion of highly mutated germinal-center b cells. *N. Engl. J. Med.* **1997**, *337*, 453–458. [CrossRef] [PubMed]
18. Ushmorov, A.; Ritz, O.; Hummel, M.; Leithauser, F.; Moller, P.; Stein, H.; Wirth, T. Epigenetic silencing of the immunoglobulin heavy-chain gene in classical hodgkin lymphoma-derived cell lines contributes to the loss of immunoglobulin expression. *Blood* **2004**, *104*, 3326–3334. [CrossRef] [PubMed]
19. Hertel, C.B.; Zhou, X.G.; Hamilton-Dutoit, S.J.; Junker, S. Loss of b cell identity correlates with loss of b cell-specific transcription factors in hodgkin/reed-sternberg cells of classical hodgkin lymphoma. *Oncogene* **2002**, *21*, 4908–4920. [CrossRef] [PubMed]
20. Schwering, I.; Brauninger, A.; Klein, U.; Jungnickel, B.; Tinguely, M.; Diehl, V.; Hansmann, M.L.; Dalla-Favera, R.; Rajewsky, K.; Kuppers, R. Loss of the b-lineage-specific gene expression program in hodgkin and reed-sternberg cells of hodgkin lymphoma. *Blood* **2003**, *101*, 1505–1512. [CrossRef] [PubMed]
21. Kuppers, R.; Klein, U.; Schwering, I.; Distler, V.; Brauninger, A.; Cattoretti, G.; Tu, Y.; Stolovitzky, G.A.; Califano, A.; Hansmann, M.L.; et al. Identification of hodgkin and reed-sternberg cell-specific genes by gene expression profiling. *J. Clin. Investig.* **2003**, *111*, 529–537. [CrossRef] [PubMed]
22. Tiacci, E.; Doring, C.; Brune, V.; van Noesel, C.J.; Klapper, W.; Mechtersheimer, G.; Falini, B.; Kuppers, R.; Hansmann, M.L. Analyzing primary hodgkin and reed-sternberg cells to capture the molecular and cellular pathogenesis of classical hodgkin lymphoma. *Blood* **2012**, *120*, 4609–4620. [CrossRef] [PubMed]
23. Steidl, C.; Diepstra, A.; Lee, T.; Chan, F.C.; Farinha, P.; Tan, K.; Telenius, A.; Barclay, L.; Shah, S.P.; Connors, J.M.; et al. Gene expression profiling of microdissected hodgkin reed-sternberg cells correlates with treatment outcome in classical hodgkin lymphoma. *Blood* **2012**, *120*, 3530–3540. [CrossRef] [PubMed]
24. Bargou, R.C.; Leng, C.; Krappmann, D.; Emmerich, F.; Mapara, M.Y.; Bommert, K.; Royer, H.D.; Scheidereit, C.; Dorken, B. High-level nuclear nf-kappa b and oct-2 is a common feature of cultured hodgkin/reed-sternberg cells. *Blood* **1996**, *87*, 4340–4347. [PubMed]
25. Carbone, A.; Gloghini, A.; Gattei, V.; Aldinucci, D.; Degan, M.; De Paoli, P.; Zagonel, V.; Pinto, A. Expression of functional cd40 antigen on reed-sternberg cells and hodgkin's disease cell lines. *Blood* **1995**, *85*, 780–789. [PubMed]
26. Fiumara, P.; Snell, V.; Li, Y.; Mukhopadhyay, A.; Younes, M.; Gillenwater, A.M.; Cabanillas, F.; Aggarwal, B.B.; Younes, A. Functional expression of receptor activator of nuclear factor kappab in hodgkin disease cell lines. *Blood* **2001**, *98*, 2784–2790. [CrossRef] [PubMed]

27. Horie, R.; Watanabe, T.; Morishita, Y.; Ito, K.; Ishida, T.; Kanegae, Y.; Saito, I.; Higashihara, M.; Mori, S.; Kadin, M.E.; et al. Ligand-independent signaling by overexpressed cd30 drives nf-kappab activation in hodgkin-reed-sternberg cells. *Oncogene* **2002**, *21*, 2493–2503. [CrossRef] [PubMed]
28. Chiu, A.; Xu, W.; He, B.; Dillon, S.R.; Gross, J.A.; Sievers, E.; Qiao, X.; Santini, P.; Hyjek, E.; Lee, J.W.; et al. Hodgkin lymphoma cells express taci and bcma receptors and generate survival and proliferation signals in response to baff and april. *Blood* **2007**, *109*, 729–739. [CrossRef] [PubMed]
29. Carbone, A.; Gloghini, A.; Gruss, H.J.; Pinto, A. Cd40 ligand is constitutively expressed in a subset of t cell lymphomas and on the microenvironmental reactive t cells of follicular lymphomas and hodgkin's disease. *Am. J. Pathol.* **1995**, *147*, 912–922. [PubMed]
30. Pinto, A.; Aldinucci, D.; Gloghini, A.; Zagonel, V.; Degan, M.; Perin, V.; Todesco, M.; De Iuliis, A.; Improta, S.; Sacco, C.; et al. The role of eosinophils in the pathobiology of hodgkin's disease. *Ann. Oncol.* **1997**, *8* (Suppl. 2), 89–96. [CrossRef] [PubMed]
31. Kreher, S.; Bouhlel, M.A.; Cauchy, P.; Lamprecht, B.; Li, S.; Grau, M.; Hummel, F.; Kochert, K.; Anagnostopoulos, I.; Johrens, K.; et al. Mapping of transcription factor motifs in active chromatin identifies irf5 as key regulator in classical hodgkin lymphoma. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, E4513–E4522. [CrossRef] [PubMed]
32. Schwarzer, R.; Dorken, B.; Jundt, F. Notch is an essential upstream regulator of nf-kappab and is relevant for survival of hodgkin and reed-sternberg cells. *Leukemia* **2012**, *26*, 806–813. [CrossRef] [PubMed]
33. Barth, T.F.; Martin-Subero, J.I.; Joos, S.; Menz, C.K.; Hasel, C.; Mechtersheimer, G.; Parwaresch, R.M.; Lichter, P.; Siebert, R.; Mooller, P. Gains of 2p involving the rel locus correlate with nuclear c-rel protein accumulation in neoplastic cells of classical hodgkin lymphoma. *Blood* **2003**, *101*, 3681–3686. [CrossRef] [PubMed]
34. Joos, S.; Granzow, M.; Holtgreve-Grez, H.; Siebert, R.; Harder, L.; Martin-Subero, J.I.; Wolf, J.; Adamowicz, M.; Barth, T.F.; Lichter, P.; et al. Hodgkin's lymphoma cell lines are characterized by frequent aberrations on chromosomes 2p and 9p including rel and jak2. *Int. J. Cancer* **2003**, *103*, 489–495. [CrossRef] [PubMed]
35. Martin-Subero, J.I.; Gesk, S.; Harder, L.; Sonoki, T.; Tucker, P.W.; Schlegelberger, B.; Grote, W.; Novo, F.J.; Calasanz, M.J.; Hansmann, M.L.; et al. Recurrent involvement of the rel and bcl11a loci in classical hodgkin lymphoma. *Blood* **2002**, *99*, 1474–1477. [CrossRef] [PubMed]
36. Steidl, C.; Telenius, A.; Shah, S.P.; Farinha, P.; Barclay, L.; Boyle, M.; Connors, J.M.; Horsman, D.E.; Gascoyne, R.D. Genome-wide copy number analysis of hodgkin reed-sternberg cells identifies recurrent imbalances with correlations to treatment outcome. *Blood* **2010**, *116*, 418–427. [CrossRef] [PubMed]
37. Cabannes, E.; Khan, G.; Aillet, F.; Jarrett, R.F.; Hay, R.T. Mutations in the ikba gene in hodgkin's disease suggest a tumour suppressor role for ikappabalpha. *Oncogene* **1999**, *18*, 3063–3070. [CrossRef] [PubMed]
38. Emmerich, F.; Meiser, M.; Hummel, M.; Demel, G.; Foss, H.D.; Jundt, F.; Mathas, S.; Krappmann, D.; Scheidereit, C.; Stein, H.; et al. Overexpression of i kappa b alpha without inhibition of nf-kappab activity and mutations in the i kappa b alpha gene in reed-sternberg cells. *Blood* **1999**, *94*, 3129–3134. [PubMed]
39. Jungnickel, B.; Staratschek-Jox, A.; Brauninger, A.; Spieker, T.; Wolf, J.; Diehl, V.; Hansmann, M.L.; Rajewsky, K.; Kuppers, R. Clonal deleterious mutations in the ikappabalpha gene in the malignant cells in hodgkin's lymphoma. *J. Exp. Med.* **2000**, *191*, 395–402. [CrossRef] [PubMed]
40. Emmerich, F.; Theurich, S.; Hummel, M.; Haeffker, A.; Vry, M.S.; Dohner, K.; Bommert, K.; Stein, H.; Dorken, B. Inactivating i kappa b epsilon mutations in hodgkin/reed-sternberg cells. *J. Pathol.* **2003**, *201*, 413–420. [CrossRef] [PubMed]
41. Lake, A.; Shield, L.A.; Cordano, P.; Chui, D.T.; Osborne, J.; Crae, S.; Wilson, K.S.; Tosi, S.; Knight, S.J.; Gesk, S.; et al. Mutations of nfkbia, encoding ikappab alpha, are a recurrent finding in classical hodgkin lymphoma but are not a unifying feature of non-ebv-associated cases. *Int. J. Cancer* **2009**, *125*, 1334–1342. [CrossRef] [PubMed]
42. Martin-Subero, J.I.; Wlodarska, I.; Bastard, C.; Picquenot, J.M.; Hoppner, J.; Giefing, M.; Klapper, W.; Siebert, R. Chromosomal rearrangements involving the bcl3 locus are recurrent in classical hodgkin and peripheral t-cell lymphoma. *Blood* **2006**, *108*, 401–402. [CrossRef] [PubMed]
43. Mathas, S.; Johrens, K.; Joos, S.; Lietz, A.; Hummel, F.; Janz, M.; Jundt, F.; Anagnostopoulos, I.; Bommert, K.; Lichter, P.; et al. Elevated nf-kappab p50 complex formation and bcl-3 expression in classical hodgkin, anaplastic large-cell, and other peripheral t-cell lymphomas. *Blood* **2005**, *106*, 4287–4293. [CrossRef] [PubMed]

44. Schmitz, R.; Hansmann, M.L.; Bohle, V.; Martin-Subero, J.I.; Hartmann, S.; Mechtersheimer, G.; Klapper, W.; Vater, I.; Giefing, M.; Gesk, S.; et al. Tnfaip3 (a20) is a tumor suppressor gene in hodgkin lymphoma and primary mediastinal b cell lymphoma. *J. Exp. Med.* **2009**, *206*, 981–989. [CrossRef] [PubMed]
45. Reichel, J.; Chadburn, A.; Rubinstein, P.G.; Giulino-Roth, L.; Tam, W.; Liu, Y.; Gaiolla, R.; Eng, K.; Brody, J.; Inghirami, G.; et al. Flow sorting and exome sequencing reveal the oncogenome of primary hodgkin and reed-sternberg cells. *Blood* **2015**, *125*, 1061–1072. [CrossRef] [PubMed]
46. Ranuncolo, S.M.; Pittaluga, S.; Evbuomwan, M.O.; Jaffe, E.S.; Lewis, B.A. Hodgkin lymphoma requires stabilized nik and constitutive relb expression for survival. *Blood* **2012**, *120*, 3756–3763. [CrossRef] [PubMed]
47. Otto, C.; Giefing, M.; Massow, A.; Vater, I.; Gesk, S.; Schlesner, M.; Richter, J.; Klapper, W.; Hansmann, M.L.; Siebert, R.; et al. Genetic lesions of the traf3 and map3k14 genes in classical hodgkin lymphoma. *Br. J. Haematol.* **2012**, *157*, 702–708. [CrossRef] [PubMed]
48. Cattaruzza, L.; Gloghini, A.; Olivo, K.; Di Francia, R.; Lorenzon, D.; De Filippi, R.; Carbone, A.; Colombatti, A.; Pinto, A.; Aldinucci, D. Functional coexpression of interleukin (il)-7 and its receptor (il-7r) on hodgkin and reed-sternberg cells: Involvement of il-7 in tumor cell growth and microenvironmental interactions of hodgkin's lymphoma. *Int. J. Cancer* **2009**, *125*, 1092–1101. [CrossRef] [PubMed]
49. Skinnider, B.F.; Elia, A.J.; Gascoyne, R.D.; Trumper, L.H.; von Bonin, F.; Kapp, U.; Patterson, B.; Snow, B.E.; Mak, T.W. Interleukin 13 and interleukin 13 receptor are frequently expressed by hodgkin and reed-sternberg cells of hodgkin lymphoma. *Blood* **2001**, *97*, 250–255. [CrossRef] [PubMed]
50. Kapp, U.; Yeh, W.-C.; Patterson, B.; Elia, A.J.; Kägi, D.; Ho, A.; Hessel, A.; Tipsword, M.; Williams, A.; Mirtsos, C.; et al. Interleukin 13 is secreted by and stimulates the growth of hodgkin and reed-sternberg cells. *J. Exp. Med.* **1999**, *189*, 1939–1946. [CrossRef] [PubMed]
51. Gruss, H.J.; Brach, M.A.; Drexler, H.G.; Bross, K.J.; Herrmann, F. Interleukin-9 is expressed by primary and cultured hodgkin and reed-sternberg cells. *Cancer Res.* **1992**, *52*, 1026–1031. [PubMed]
52. Aldinucci, D.; Poletto, D.; Gloghini, A.; Nanni, P.; Degan, M.; Perin, T.; Ceolin, P.; Rossi, F.M.; Gattei, V.; Carbone, A.; et al. Expression of functional interleukin-3 receptors on hodgkin and reed-sternberg cells. *Am. J. Pathol.* **2002**, *160*, 585–596. [CrossRef]
53. Lamprecht, B.; Kreher, S.; Anagnostopoulos, I.; Johrens, K.; Monteleone, G.; Jundt, F.; Stein, H.; Janz, M.; Dorken, B.; Mathas, S. Aberrant expression of the th2 cytokine il-21 in hodgkin lymphoma cells regulates stat3 signaling and attracts treg cells via regulation of mip-3alpha. *Blood* **2008**, *112*, 3339–3347. [CrossRef] [PubMed]
54. Scheeren, F.A.; Diehl, S.A.; Smit, L.A.; Beaumont, T.; Naspetti, M.; Bende, R.J.; Blom, B.; Karube, K.; Ohshima, K.; van Noesel, C.J.; et al. Il-21 is expressed in hodgkin lymphoma and activates stat5: Evidence that activated stat5 is required for hodgkin lymphomagenesis. *Blood* **2008**, *111*, 4706–4715. [CrossRef] [PubMed]
55. Hinz, M.; Lemke, P.; Anagnostopoulos, I.; Hacker, C.; Krappmann, D.; Mathas, S.; Dörken, B.; Zenke, M.; Stein, H.; Scheidereit, C. Nuclear factor κb–dependent gene expression profiling of hodgkin's disease tumor cells, pathogenetic significance, and link to constitutive signal transducer and activator of transcription 5a activity. *J. Exp. Med.* **2002**, *196*, 605–617. [CrossRef] [PubMed]
56. Skinnider, B.F.; Elia, A.J.; Gascoyne, R.D.; Patterson, B.; Trumper, L.; Kapp, U.; Mak, T.W. Signal transducer and activator of transcription 6 is frequently activated in hodgkin and reed-sternberg cells of hodgkin lymphoma. *Blood* **2002**, *99*, 618–626. [CrossRef] [PubMed]
57. Kube, D.; Holtick, U.; Vockerodt, M.; Ahmadi, T.; Haier, B.; Behrmann, I.; Heinrich, P.C.; Diehl, V.; Tesch, H. Stat3 is constitutively activated in hodgkin cell lines. *Blood* **2001**, *98*, 762–770. [CrossRef] [PubMed]
58. Joos, S.; Kupper, M.; Ohl, S.; von Bonin, F.; Mechtersheimer, G.; Bentz, M.; Marynen, P.; Moller, P.; Pfreundschuh, M.; Trumper, L.; et al. Genomic imbalances including amplification of the tyrosine kinase gene jak2 in cd30+ hodgkin cells. *Cancer Res.* **2000**, *60*, 549–552. [PubMed]
59. Weniger, M.A.; Melzner, I.; Menz, C.K.; Wegener, S.; Bucur, A.J.; Dorsch, K.; Mattfeldt, T.; Barth, T.F.; Moller, P. Mutations of the tumor suppressor gene socs-1 in classical hodgkin lymphoma are frequent and associated with nuclear phospho-stat5 accumulation. *Oncogene* **2006**, *25*, 2679–2684. [CrossRef] [PubMed]
60. Gunawardana, J.; Chan, F.C.; Telenius, A.; Woolcock, B.; Kridel, R.; Tan, K.L.; Ben-Neriah, S.; Mottok, A.; Lim, R.S.; Boyle, M.; et al. Recurrent somatic mutations of ptpn1 in primary mediastinal b cell lymphoma and hodgkin lymphoma. *Nat. Genet.* **2014**, *46*, 329–335. [CrossRef] [PubMed]

61. Tiacci, E.; Penson, A.; Schiavoni, G.; Ladewig, E.; Fortini, E.; Wang, Y.C.; Spanhol-Rosseto, A.; Venanzi, A.; Gianni, A.M.; Viviani, S.; et al. New recurrently mutated genes in classical hodgkin lymphoma revealed by whole-exome sequencing of microdissected tumor cells. *Blood* **2016**, *128*, 1088.
62. Zahn, M.; Marienfeld, R.; Melzner, I.; Heinrich, J.; Renner, B.; Wegener, S.; Miessner, A.; Barth, T.F.; Dorsch, K.; Bruderlein, S.; et al. A novel ptpn1 splice variant upregulates jak/stat activity in classical hodgkin lymphoma cells. *Blood* **2017**, *129*, 1480–1490. [CrossRef] [PubMed]
63. Lollies, A.; Hartmann, S.; Schneider, M.; Bracht, T.; Weiss, A.L.; Arnolds, J.; Klein-Hitpass, L.; Sitek, B.; Hansmann, M.L.; Kuppers, R.; et al. An oncogenic axis of stat-mediated batf3 upregulation causing myc activity in classical hodgkin lymphoma and anaplastic large cell lymphoma. *Leukemia* **2018**, *32*, 92–101. [CrossRef] [PubMed]
64. Mathas, S.; Hinz, M.; Anagnostopoulos, I.; Krappmann, D.; Lietz, A.; Jundt, F.; Bommert, K.; Mechta-Grigoriou, F.; Stein, H.; Dorken, B.; et al. Aberrantly expressed c-jun and junb are a hallmark of hodgkin lymphoma cells, stimulate proliferation and synergize with nf-kappa b. *EMBO J.* **2002**, *21*, 4104–4113. [CrossRef] [PubMed]
65. Dutton, A.; Reynolds, G.M.; Dawson, C.W.; Young, L.S.; Murray, P.G. Constitutive activation of phosphatidyl-inositide 3 kinase contributes to the survival of hodgkin's lymphoma cells through a mechanism involving akt kinase and mtor. *J. Pathol.* **2005**, *205*, 498–506. [CrossRef] [PubMed]
66. Georgakis, G.V.; Li, Y.; Rassidakis, G.Z.; Medeiros, L.J.; Mills, G.B.; Younes, A. Inhibition of the phosphatidylinositol-3 kinase/akt promotes g1 cell cycle arrest and apoptosis in hodgkin lymphoma. *Br. J. Haematol.* **2006**, *132*, 503–511. [CrossRef] [PubMed]
67. Vrzalikova, K.; Ibrahim, M.; Vockerodt, M.; Perry, T.; Margielewska, S.; Lupino, L.; Nagy, E.; Soilleux, E.; Liebelt, D.; Hollows, R.; et al. S1pr1 drives a feed forward signalling loop to regulate batf3 and the transcriptional programme of hodgkin lymphoma cells. *Leukemia* **2017**, *32*, 214. [CrossRef] [PubMed]
68. Willenbrock, K.; Kuppers, R.; Renne, C.; Brune, V.; Eckerle, S.; Weidmann, E.; Brauninger, A.; Hansmann, M.L. Common features and differences in the transcriptome of large cell anaplastic lymphoma and classical hodgkin's lymphoma. *Haematologica* **2006**, *91*, 596–604. [PubMed]
69. Renne, C.; Minner, S.; Kuppers, R.; Hansmann, M.L.; Brauninger, A. Autocrine ngfbeta/trka signalling is an important survival factor for hodgkin lymphoma derived cell lines. *Leuk. Res.* **2008**, *32*, 163–167. [CrossRef] [PubMed]
70. Renne, C.; Willenbrock, K.; Kuppers, R.; Hansmann, M.L.; Brauninger, A. Autocrine- and paracrine-activated receptor tyrosine kinases in classic hodgkin lymphoma. *Blood* **2005**, *105*, 4051–4059. [CrossRef] [PubMed]
71. Cader, F.Z.; Vockerodt, M.; Bose, S.; Nagy, E.; Brundler, M.A.; Kearns, P.; Murray, P.G. The ebv oncogene lmp1 protects lymphoma cells from cell death through the collagen-mediated activation of ddr1. *Blood* **2013**, *122*, 4237–4245. [CrossRef] [PubMed]
72. Levine, P.H.; Ablashi, D.V.; Berard, C.W.; Carbone, P.P.; Waggoner, D.E.; Malan, L. Elevated antibody titers to epstein-barr virus in hodgkin's disease. *Cancer* **1971**, *27*, 416–421. [CrossRef]
73. Mueller, N.; Evans, A.; Harris, N.L.; Comstock, G.W.; Jellum, E.; Magnus, K.; Orentreich, N.; Polk, B.F.; Vogelman, J. Hodgkin's disease and epstein-barr virus. Altered antibody pattern before diagnosis. *N. Engl. J. Med.* **1989**, *320*, 689–695. [CrossRef] [PubMed]
74. Connelly, R.R.; Christine, B.W. A cohort study of cancer following infectious mononucleosis. *Cancer Res.* **1974**, *34*, 1172–1178. [PubMed]
75. Rosdahl, N.; Larsen, S.O.; Clemmesen, J. Hodgkin's disease in patients with previous infectious mononucleosis: 30 years' experience. *BMJ* **1974**, *2*, 253–256. [CrossRef] [PubMed]
76. Hjalgrim, H.; Smedby, K.E.; Rostgaard, K.; Molin, D.; Hamilton-Dutoit, S.; Chang, E.T.; Ralfkiaer, E.; Sundstrom, C.; Adami, H.O.; Glimelius, B.; et al. Infectious mononucleosis, childhood social environment, and risk of hodgkin lymphoma. *Cancer Res.* **2007**, *67*, 2382–2388. [CrossRef] [PubMed]
77. Hjalgrim, H.; Munksgaard, L.; Melbye, M. Epstein-barr virus and hodgkin's lymphoma. *Ugeskr Laeger* **2002**, *164*, 5924–5927. [PubMed]
78. Poppema, S.; van Imhoff, G.; Torensma, R.; Smit, J. Lymphadenopathy morphologically consistent with hodgkin's disease associated with epstein-barr virus infection. *Am. J. Clin. Pathol.* **1985**, *84*, 385–390. [CrossRef] [PubMed]
79. Weiss, L.M.; Strickler, J.G.; Warnke, R.A.; Purtilo, D.T.; Sklar, J. Epstein-barr viral DNA in tissues of hodgkin's disease. *Am. J. Pathol.* **1987**, *129*, 86–91. [PubMed]

80. Anagnostopoulos, I.; Herbst, H.; Niedobitek, G.; Stein, H. Demonstration of monoclonal ebv genomes in hodgkin's disease and ki-1-positive anaplastic large cell lymphoma by combined southern blot and in situ hybridization. *Blood* **1989**, *74*, 810–816. [PubMed]
81. Weiss, L.M.; Movahed, L.A.; Warnke, R.A.; Sklar, J. Detection of epstein-barr viral genomes in reed-sternberg cells of hodgkin's disease. *N. Engl. J. Med.* **1989**, *320*, 502–506. [CrossRef] [PubMed]
82. Wu, T.-C.; Mann, R.B.; Charache, P.; Hayward, S.D.; Staal, S.; Lambe, B.C.; Ambinder, R.F. Detection of ebv gene expression in reed-sternberg cells of hodgkin's disease. *Int. J. Cancer* **1990**, *46*, 801–804. [CrossRef] [PubMed]
83. Coates, P.J.; Slavin, G.; D'Ardenne, A.J. Persistence of epstein-barr virus in reed-sternberg cells throughout the course of hodgkin's disease. *J. Pathol.* **1991**, *164*, 291–297. [CrossRef] [PubMed]
84. Glaser, S.L.; Lin, R.J.; Stewart, S.L.; Ambinder, R.F.; Jarrett, R.F.; Brousset, P.; Pallesen, G.; Gulley, M.L.; Khan, G.; O'Grady, J.; et al. Epstein-barr virus-associated hodgkin's disease: Epidemiologic characteristics in international data. *Int. J. Cancer* **1997**, *70*, 375–382. [CrossRef]
85. Glaser, S.L.; Jarrett, R.F. The epidemiology of Hodgkin's disease. *Baillieres Clin. Haematol.* **1996**, *9*, 401–416. [CrossRef]
86. Chang, K.L.; Albujar, P.F.; Chen, Y.Y.; Johnson, R.M.; Weiss, L.M. High prevalence of epstein-barr virus in the reed-sternberg cells of hodgkin's disease occurring in peru. *Blood* **1993**, *81*, 496–501. [PubMed]
87. Weinreb, M.; Day, P.J.; Niggli, F.; Green, E.K.; Nyong'o, A.O.; Othieno-Abinya, N.A.; Riyat, M.S.; Raafat, F.; Mann, J.R. The consistent association between epstein-barr virus and hodgkin's disease in children in kenya. *Blood* **1996**, *87*, 3828–3836. [PubMed]
88. Armstrong, A.A.; Alexander, F.E.; Cartwright, R.; Angus, B.; Krajewski, A.S.; Wright, D.H.; Brown, I.; Lee, F.; Kane, E.; Jarrett, R.F. Epstein-barr virus and hodgkin's disease: Further evidence for the three disease hypothesis. *Leukemia* **1998**, *12*, 1272–1276. [CrossRef] [PubMed]
89. Jarrett, R.F.; Gallagher, A.; Jones, D.B.; Alexander, F.E.; Krajewski, A.S.; Kelsey, A.; Adams, J.; Angus, B.; Gledhill, S.; Wright, D.H.; et al. Detection of epstein-barr virus genomes in hodgkin's disease: Relation to age. *J. Clin. Pathol.* **1991**, *44*, 844–848. [CrossRef] [PubMed]
90. Flavell, K.J.; Biddulph, J.P.; Powell, J.E.; Parkes, S.E.; Redfern, D.; Weinreb, M.; Nelson, P.; Mann, J.R.; Young, L.S.; Murray, P.G. South asian ethnicity and material deprivation increase the risk of epstein-barr virus infection in childhood hodgkin's disease. *Br. J. Cancer* **2001**, *85*, 350–356. [CrossRef] [PubMed]
91. Westhoff Smith, D.; Sugden, B. Potential cellular functions of epstein-barr nuclear antigen 1 (ebna1) of epstein-barr virus. *Viruses* **2013**, *5*, 226–240. [CrossRef] [PubMed]
92. Frappier, L. Contributions of epstein-barr nuclear antigen 1 (ebna1) to cell immortalization and survival. *Viruses* **2012**, *4*, 1537–1547. [CrossRef] [PubMed]
93. Frappier, L. Ebna1 and host factors in epstein-barr virus latent DNA replication. *Curr. Opin. Virol.* **2012**, *2*, 733–739. [CrossRef] [PubMed]
94. Frappier, L. The epstein-barr virus ebna1 protein. *Scientifica (Cairo)* **2012**, *2012*, 438204. [CrossRef] [PubMed]
95. Kennedy, G.; Komano, J.; Sugden, B. Epstein-barr virus provides a survival factor to burkitt's lymphomas. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 14269–14274. [CrossRef] [PubMed]
96. Saridakis, V.; Sheng, Y.; Sarkari, F.; Holowaty, M.N.; Shire, K.; Nguyen, T.; Zhang, R.G.; Liao, J.; Lee, W.; Edwards, A.M.; et al. Structure of the p53 binding domain of hausp/usp7 bound to epstein-barr nuclear antigen 1 implications for ebv-mediated immortalization. *Mol. Cell.* **2005**, *18*, 25–36. [CrossRef] [PubMed]
97. Kube, D.; Vockerodt, M.; Weber, O.; Hell, K.; Wolf, J.; Haier, B.; Grasser, F.A.; Muller-Lantzsch, N.; Kieff, E.; Diehl, V.; et al. Expression of epstein-barr virus nuclear antigen 1 is associated with enhanced expression of cd25 in the hodgkin cell line l428. *J. Virol.* **1999**, *73*, 1630–1636. [PubMed]
98. Flavell, J.R.; Baumforth, K.R.; Wood, V.H.; Davies, G.L.; Wei, W.; Reynolds, G.M.; Morgan, S.; Boyce, A.; Kelly, G.L.; Young, L.S.; et al. Down-regulation of the tgf-beta target gene, ptprk, by the epstein-barr virus encoded ebna1 contributes to the growth and survival of hodgkin lymphoma cells. *Blood* **2008**, *111*, 292–301. [CrossRef] [PubMed]
99. Wood, V.H.; O'Neil, J.D.; Wei, W.; Stewart, S.E.; Dawson, C.W.; Young, L.S. Epstein-barr virus-encoded ebna1 regulates cellular gene transcription and modulates the stat1 and tgfbeta signaling pathways. *Oncogene* **2007**, *26*, 4135–4147. [CrossRef] [PubMed]

100. Baumforth, K.R.; Birgersdotter, A.; Reynolds, G.M.; Wei, W.; Kapatai, G.; Flavell, J.R.; Kalk, E.; Piper, K.; Lee, S.; Machado, L.; et al. Expression of the epstein-barr virus-encoded epstein-barr virus nuclear antigen 1 in hodgkin's lymphoma cells mediates up-regulation of ccl20 and the migration of regulatory t cells. *Am. J. Pathol.* **2008**, *173*, 195–204. [CrossRef] [PubMed]
101. Wilson, J.B.; Bell, J.L.; Levine, A.J. Expression of epstein-barr virus nuclear antigen-1 induces b cell neoplasia in transgenic mice. *EMBO J.* **1996**, *15*, 3117–3126. [PubMed]
102. Tsimbouri, P.; Drotar, M.E.; Coy, J.L.; Wilson, J.B. Bcl-xl and rag genes are induced and the response to il-2 enhanced in emuebna-1 transgenic mouse lymphocytes. *Oncogene* **2002**, *21*, 5182–5187. [CrossRef] [PubMed]
103. Kang, M.S.; Lu, H.; Yasui, T.; Sharpe, A.; Warren, H.; Cahir-McFarland, E.; Bronson, R.; Hung, S.C.; Kieff, E. Epstein-barr virus nuclear antigen 1 does not induce lymphoma in transgenic fvb mice. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 820–825. [CrossRef] [PubMed]
104. Coppotelli, G.; Mughal, N.; Callegari, S.; Sompallae, R.; Caja, L.; Luijsterburg, M.S.; Dantuma, N.P.; Moustakas, A.; Masucci, M.G. The epstein-barr virus nuclear antigen-1 reprograms transcription by mimicry of high mobility group a proteins. *Nucleic Acids Res.* **2013**, *41*, 2950–2962. [CrossRef] [PubMed]
105. Dresang, L.R.; Vereide, D.T.; Sugden, B. Identifying sites bound by epstein-barr virus nuclear antigen 1 (ebna1) in the human genome: Defining a position-weighted matrix to predict sites bound by ebna1 in viral genomes. *J. Virol.* **2009**, *83*, 2930–2940. [CrossRef] [PubMed]
106. Lu, F.; Wikramasinghe, P.; Norseen, J.; Tsai, K.; Wang, P.; Showe, L.; Davuluri, R.V.; Lieberman, P.M. Genome-wide analysis of host-chromosome binding sites for epstein-barr virus nuclear antigen 1 (ebna1). *Virol. J.* **2010**, *7*, 262. [CrossRef] [PubMed]
107. Canaan, A.; Haviv, I.; Urban, A.E.; Schulz, V.P.; Hartman, S.; Zhang, Z.; Palejev, D.; Deisseroth, A.B.; Lacy, J.; Snyder, M.; et al. Ebna1 regulates cellular gene expression by binding cellular promoters. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 22421–22426. [CrossRef] [PubMed]
108. Tempera, I.; De Leo, A.; Kossenkov, A.V.; Cesaroni, M.; Song, H.; Dawany, N.; Showe, L.; Lu, F.; Wikramasinghe, P.; Lieberman, P.M. Identification of mef2b, ebf1, and il6r as direct gene targets of epstein-barr virus (ebv) nuclear antigen 1 critical for ebv-infected b-lymphocyte survival. *J. Virol.* **2016**, *90*, 345–355. [CrossRef] [PubMed]
109. Li, N.; Thompson, S.; Schultz, D.C.; Zhu, W.; Jiang, H.; Luo, C.; Lieberman, P.M. Discovery of selective inhibitors against ebna1 via high throughput in silico virtual screening. *PLoS ONE* **2010**, *5*, e10126. [CrossRef] [PubMed]
110. Thompson, S.; Messick, T.; Schultz, D.C.; Reichman, M.; Lieberman, P.M. Development of a high-throughput screen for inhibitors of epstein-barr virus ebna1. *J. Biomol. Screen* **2010**, *15*, 1107–1115. [CrossRef] [PubMed]
111. Jiang, L.; Lui, Y.L.; Li, H.; Chan, C.F.; Lan, R.; Chan, W.L.; Lau, T.C.; Tsao, G.S.; Mak, N.K.; Wong, K.L. Ebna1-specific luminescent small molecules for the imaging and inhibition of latent ebv-infected tumor cells. *Chem. Commun.* **2014**, *50*, 6517–6519. [CrossRef] [PubMed]
112. Taylor, G.S.; Jia, H.; Harrington, K.; Lee, L.W.; Turner, J.; Ladell, K.; Price, D.A.; Tanday, M.; Matthews, J.; Roberts, C.; et al. A recombinant modified vaccinia ankara vaccine encoding epstein-barr virus (ebv) target antigens: A phase i trial in uk patients with ebv-positive cancer. *Clin. Cancer Res.* **2014**, *20*, 5009–5022. [CrossRef] [PubMed]
113. Jones, K.; Nourse, J.P.; Morrison, L.; Nguyen-Van, D.; Moss, D.J.; Burrows, S.R.; Gandhi, M.K. Expansion of ebna1-specific effector t cells in posttransplantation lymphoproliferative disorders. *Blood* **2010**, *116*, 2245–2252. [CrossRef] [PubMed]
114. Icheva, V.; Kayser, S.; Wolff, D.; Tuve, S.; Kyzirakos, C.; Bethge, W.; Greil, J.; Albert, M.H.; Schwinger, W.; Nathrath, M.; et al. Adoptive transfer of epstein-barr virus (ebv) nuclear antigen 1-specific t cells as treatment for ebv reactivation and lymphoproliferative disorders after allogeneic stem-cell transplantation. *J. Clin. Oncol.* **2013**, *31*, 39–48. [CrossRef] [PubMed]
115. Lista, M.J.; Martins, R.P.; Billant, O.; Contesse, M.A.; Findakly, S.; Pochard, P.; Daskalogianni, C.; Beauvineau, C.; Guetta, C.; Jamin, C.; et al. Nucleolin directly mediates epstein-barr virus immune evasion through binding to g-quadruplexes of ebna1 mrna. *Nat. Commun.* **2017**, *8*, 16043. [CrossRef] [PubMed]
116. Lam, N.; Sugden, B. Cd40 and its viral mimic, lmp1: Similar means to different ends. *Cell. Signal.* **2003**, *15*, 9–16. [CrossRef]
117. Kaykas, A.; Worringer, K.; Sugden, B. Cd40 and lmp-1 both signal from lipid rafts but lmp-1 assembles a distinct, more efficient signaling complex. *Embo J.* **2001**, *20*, 2641–2654. [CrossRef] [PubMed]

118. Bishop, G.A.; Hostager, B.S. Signaling by cd40 and its mimics in b cell activation. *Immunol. Res.* **2001**, *24*, 97–110. [CrossRef]
119. Panagopoulos, D.; Victoratos, P.; Alexiou, M.; Kollias, G.; Mosialos, G. Comparative analysis of signal transduction by cd40 and the epstein-barr virus oncoprotein lmp1 in vivo. *J. Virol.* **2004**, *78*, 13253–13261. [CrossRef] [PubMed]
120. Kilger, E.; Kieser, A.; Baumann, M.; Hammerschmidt, W. Epstein-barr virus-mediated b-cell proliferation is dependent upon latent membrane protein 1, which simulates an activated cd40 receptor. *EMBO J.* **1998**, *17*, 1700–1709. [CrossRef] [PubMed]
121. Gires, O.; Kohlhuber, F.; Kilger, E.; Baumann, M.; Kieser, A.; Kaiser, C.; Zeidler, R.; Scheffer, B.; Ueffing, M.; Hammerschmidt, W. Latent membrane protein 1 of epstein-barr virus interacts with jak3 and activates stat proteins. *EMBO J.* **1999**, *18*, 3064–3073. [CrossRef] [PubMed]
122. Eliopoulos, A.G.; Young, L.S. Activation of the cjun n-terminal kinase (jnk) pathway by the epstein-barr virus-encoded latent membrane protein 1 (lmp1). *Oncogene* **1998**, *16*, 1731–1742. [CrossRef] [PubMed]
123. Laherty, C.D.; Hu, H.M.; Opipari, A.W.; Wang, F.; Dixit, V.M. The epstein-barr virus lmp1 gene product induces a20 zinc finger protein expression by activating nuclear factor kappa b. *J. Biol. Chem.* **1992**, *267*, 24157–24160. [PubMed]
124. Huen, D.S.; Henderson, S.A.; Croom-Carter, D.; Rowe, M. The epstein-barr virus latent membrane protein-1 (lmp1) mediates activation of nf-kappa b and cell surface phenotype via two effector regions in its carboxy-terminal cytoplasmic domain. *Oncogene* **1995**, *10*, 549–560. [PubMed]
125. Schumacher, M.A.; Schmitz, R.; Brune, V.; Tiacci, E.; Doring, C.; Hansmann, M.L.; Siebert, R.; Kuppers, R. Mutations in the genes coding for the nf-kappab regulating factors ikappabalpha and a20 are uncommon in nodular lymphocyte-predominant hodgkin's lymphoma. *Haematologica* **2010**, *95*, 153–157. [CrossRef] [PubMed]
126. Etzel, B.M.; Gerth, M.; Chen, Y.; Wunsche, E.; Facklam, T.; Beck, J.F.; Guntinas-Lichius, O.; Petersen, I. Mutation analysis of tumor necrosis factor alpha-induced protein 3 gene in hodgkin lymphoma. *Pathol. Res. Pract.* **2017**, *213*, 256–260. [CrossRef] [PubMed]
127. Vockerodt, M.; Morgan, S.L.; Kuo, M.; Wei, W.; Chukwuma, M.B.; Arrand, J.R.; Kube, D.; Gordon, J.; Young, L.S.; Woodman, C.B.; et al. The epstein-barr virus oncoprotein, latent membrane protein-1, reprograms germinal centre b cells towards a hodgkin's reed-sternberg-like phenotype. *J. Pathol.* **2008**, *216*, 83–92. [CrossRef] [PubMed]
128. Anderton, J.A.; Bose, S.; Vockerodt, M.; Vrzalikova, K.; Wei, W.; Kuo, M.; Helin, K.; Christensen, J.; Rowe, M.; Murray, P.G.; et al. The h3k27me3 demethylase, kdm6b, is induced by epstein-barr virus and over-expressed in hodgkin's lymphoma. *Oncogene* **2011**, *30*, 2037–2043. [CrossRef] [PubMed]
129. Leonard, S.; Gordon, N.; Smith, N.; Rowe, M.; Murray, P.G.; Woodman, C.B. Arginine methyltransferases are regulated by epstein-barr virus in b cells and are differentially expressed in hodgkin's lymphoma. *Pathogens* **2012**, *1*, 52–64. [CrossRef] [PubMed]
130. Leonard, S.; Wei, W.; Anderton, J.; Vockerodt, M.; Rowe, M.; Murray, P.G.; Woodman, C.B. Epigenetic and transcriptional changes which follow epstein-barr virus infection of germinal center b cells and their relevance to the pathogenesis of hodgkin's lymphoma. *J. Virol.* **2011**, *85*, 9568–9577. [CrossRef] [PubMed]
131. Martin, K.A.; Lupey, L.N.; Tempera, I. Epstein-barr virus oncoprotein lmp1 mediates epigenetic changes in host gene expression through parp1. *J. Virol.* **2016**, *90*, 8520–8530. [CrossRef] [PubMed]
132. Motsch, N.; Pfuhl, T.; Mrazek, J.; Barth, S.; Grasser, F.A. Epstein-barr virus-encoded latent membrane protein 1 (lmp1) induces the expression of the cellular microrna mir-146a. *RNA Biol.* **2007**, *4*, 131–137. [CrossRef] [PubMed]
133. Cameron, J.E.; Yin, Q.; Fewell, C.; Lacey, M.; McBride, J.; Wang, X.; Lin, Z.; Schaefer, B.C.; Flemington, E.K. Epstein-barr virus latent membrane protein 1 induces cellular microrna mir-146a, a modulator of lymphocyte signaling pathways. *J. Virol.* **2008**, *82*, 1946–1958. [CrossRef] [PubMed]
134. Lu, F.; Weidmer, A.; Liu, C.G.; Volinia, S.; Croce, C.M.; Lieberman, P.M. Epstein-barr virus-induced mir-155 attenuates nf-kappab signaling and stabilizes latent virus persistence. *J. Virol.* **2008**, *82*, 10436–10443. [CrossRef] [PubMed]
135. Anastasiadou, E.; Boccellato, F.; Vincenti, S.; Rosato, P.; Bozzoni, I.; Frati, L.; Faggioni, A.; Presutti, C.; Trivedi, P. Epstein-barr virus encoded lmp1 downregulates tcl1 oncogene through mir-29b. *Oncogene* **2010**, *29*, 1316–1328. [CrossRef] [PubMed]

136. Li, G.; Wu, Z.; Peng, Y.; Liu, X.; Lu, J.; Wang, L.; Pan, Q.; He, M.L.; Li, X.P. Microrna-10b induced by epstein-barr virus-encoded latent membrane protein-1 promotes the metastasis of human nasopharyngeal carcinoma cells. *Cancer Lett.* **2010**, *299*, 29–36. [CrossRef] [PubMed]
137. Cahir-McFarland, E.D.; Carter, K.; Rosenwald, A.; Giltnane, J.M.; Henrickson, S.E.; Staudt, L.M.; Kieff, E. Role of nf-kappa b in cell survival and transcription of latent membrane protein 1 - expressing or epstein-barr virus latency iii-infected cells. *J. Virol.* **2004**, *78*, 4108–4119. [CrossRef] [PubMed]
138. Dutton, A.; O'Neil, J.D.; Milner, A.E.; Reynolds, G.M.; Starczynski, J.; Crocker, J.; Young, L.S.; Murray, P.G. Expression of the cellular flice-inhibitory protein (c-flip) protects hodgkin's lymphoma cells from autonomous fas-mediated death. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 6611–6616. [CrossRef] [PubMed]
139. Lajoie, V.; Lemieux, B.; Sawan, B.; Lichtensztejn, D.; Lichtensztejn, Z.; Wellinger, R.; Mai, S.; Knecht, H. Lmp1 mediates multinuclearity through downregulation of shelterin proteins and formation of telomeric aggregates. *Blood* **2015**, *125*, 2101–2110. [CrossRef] [PubMed]
140. Knecht, H.; Mai, S. Lmp1 and dynamic progressive telomere dysfunction: A major culprit in ebv-associated hodgkin's lymphoma. *Viruses* **2017**, *9*, 164. [CrossRef] [PubMed]
141. Vrzalikova, K.; Vockerodt, M.; Leonard, S.; Bell, A.; Wei, W.; Schrader, A.; Wright, K.L.; Kube, D.; Rowe, M.; Woodman, C.B.; et al. Down-regulation of blimp1α by the ebv oncogene, lmp-1, disrupts the plasma cell differentiation program and prevents viral replication in b cells: Implications for the pathogenesis of ebv-associated b-cell lymphomas. *Blood* **2011**, *117*, 5907–5917. [CrossRef] [PubMed]
142. Sueur, C.; Lupo, J.; Mas, P.; Morand, P.; Boyer, V. Difference in cytokine production and cell cycle progression induced by epstein-barr virus lmp1 deletion variants in kmh2, a hodgkin lymphoma cell line. *Virol. J.* **2014**, *11*, 94. [CrossRef] [PubMed]
143. Kis, L.L.; Takahara, M.; Nagy, N.; Klein, G.; Klein, E. Cytokine mediated induction of the major epstein-barr virus (ebv)-encoded transforming protein, lmp-1. *Immunol. Lett.* **2006**, *104*, 83–88. [CrossRef] [PubMed]
144. Dukers, D.F.; Jaspars, L.H.; Vos, W.; Oudejans, J.J.; Hayes, D.; Cillessen, S.; Middeldorp, J.M.; Meijer, C.J. Quantitative immunohistochemical analysis of cytokine profiles in epstein-barr virus-positive and -negative cases of hodgkin's disease. *J. Pathol.* **2000**, *190*, 143–149. [CrossRef]
145. Rickinson, A.B.; Moss, D.J. Human cytotoxic t lymphocyte responses to epstein-barr virus infection. *Annu. Rev. Immunol.* **1997**, *15*, 405–431. [CrossRef] [PubMed]
146. Tsang, M.L.; Munz, C. Cytolytic t lymphocytes from hla-b8+ donors frequently recognize the hodgkin's lymphoma associated latent membrane protein 2 of epstein barr virus. *Herpesviridae* **2011**, *2*, 4. [CrossRef] [PubMed]
147. Bollard, C.M.; Gottschalk, S.; Huls, M.H.; Molldrem, J.; Przepiorka, D.; Rooney, C.M.; Heslop, H.E. In vivo expansion of lmp 1- and 2-specific t-cells in a patient who received donor-derived ebv-specific t-cells after allogeneic stem cell transplantation. *Leuk. Lymphoma* **2006**, *47*, 837–842. [CrossRef] [PubMed]
148. Duraiswamy, J.; Sherritt, M.; Thomson, S.; Tellam, J.; Cooper, L.; Connolly, G.; Bharadwaj, M.; Khanna, R. Therapeutic lmp1 polyepitope vaccine for ebv-associated hodgkin disease and nasopharyngeal carcinoma. *Blood* **2003**, *101*, 3150–3156. [CrossRef] [PubMed]
149. Gottschalk, S.; Edwards, O.L.; Sili, U.; Huls, M.H.; Goltsova, T.; Davis, A.R.; Heslop, H.E.; Rooney, C.M. Generating ctls against the subdominant epstein-barr virus lmp1 antigen for the adoptive immunotherapy of ebv-associated malignancies. *Blood* **2003**, *101*, 1905–1912. [CrossRef] [PubMed]
150. Chapman, A.L.; Rickinson, A.B.; Thomas, W.A.; Jarrett, R.F.; Crocker, J.; Lee, S.P. Epstein-barr virus-specific cytotoxic t lymphocyte responses in the blood and tumor site of hodgkin's disease patients: Implications for a t-cell-based therapy. *Cancer Res.* **2001**, *61*, 6219–6226. [PubMed]
151. Khanna, R.; Burrows, S.R.; Nicholls, J.; Poulsen, L.M. Identification of cytotoxic t cell epitopes within epstein-barr virus (ebv) oncogene latent membrane protein 1 (lmp1): Evidence for hla a2 supertype-restricted immune recognition of ebv-infected cells by lmp1-specific cytotoxic t lymphocytes. *Eur. J. Immunol.* **1998**, *28*, 451–458. [CrossRef]
152. Murray, P.G.; Constandinou, C.M.; Crocker, J.; Young, L.S.; Ambinder, R.F. Analysis of major histocompatibility complex class i, tap expression, and lmp2 epitope sequence in epstein-barr virus-positive hodgkin's disease. *Blood* **1998**, *92*, 2477–2483. [PubMed]

153. Lee, S.P.; Constandinou, C.M.; Thomas, W.A.; Croom-Carter, D.; Blake, N.W.; Murray, P.G.; Crocker, J.; Rickinson, A.B. Antigen presenting phenotype of hodgkin reed-sternberg cells: Analysis of the hla class i processing pathway and the effects of interleukin-10 on epstein-barr virus-specific cytotoxic t-cell recognition. *Blood* **1998**, *92*, 1020–1030. [PubMed]
154. Tsang, C.W.; Lin, X.; Gudgeon, N.H.; Taylor, G.S.; Jia, H.; Hui, E.P.; Chan, A.T.; Lin, C.K.; Rickinson, A.B. Cd4+ t-cell responses to epstein-barr virus nuclear antigen ebna1 in chinese populations are highly focused on novel c-terminal domain-derived epitopes. *J. Virol.* **2006**, *80*, 8263–8266. [CrossRef] [PubMed]
155. Gurer, C.; Strowig, T.; Brilot, F.; Pack, M.; Trumpfheller, C.; Arrey, F.; Park, C.G.; Steinman, R.M.; Munz, C. Targeting the nuclear antigen 1 of epstein-barr virus to the human endocytic receptor dec-205 stimulates protective t-cell responses. *Blood* **2008**, *112*, 1231–1239. [CrossRef] [PubMed]
156. Chen, B.J.; Chapuy, B.; Ouyang, J.; Sun, H.H.; Roemer, M.G.; Xu, M.L.; Yu, H.; Fletcher, C.D.; Freeman, G.J.; Shipp, M.A.; et al. Pd-l1 expression is characteristic of a subset of aggressive b-cell lymphomas and virus-associated malignancies. *Clin. Cancer Res.* **2013**, *19*, 3462–3473. [CrossRef] [PubMed]
157. Green, M.R.; Rodig, S.; Juszczynski, P.; Ouyang, J.; Sinha, P.; O'Donnell, E.; Neuberg, D.; Shipp, M.A. Constitutive ap-1 activity and ebv infection induce pd-l1 in hodgkin lymphomas and posttransplant lymphoproliferative disorders: Implications for targeted therapy. *Clin. Cancer Res.* **2012**, *18*, 1611–1618. [CrossRef] [PubMed]
158. Green, M.R.; Monti, S.; Rodig, S.J.; Juszczynski, P.; Currie, T.; O'Donnell, E.; Chapuy, B.; Takeyama, K.; Neuberg, D.; Golub, T.R.; et al. Integrative analysis reveals selective 9p24.1 amplification, increased pd-1 ligand expression, and further induction via jak2 in nodular sclerosing hodgkin lymphoma and primary mediastinal large b-cell lymphoma. *Blood* **2010**, *116*, 3268–3277. [CrossRef] [PubMed]
159. Paydas, S.; Bagir, E.; Seydaoglu, G.; Ercolak, V.; Ergin, M. Programmed death-1 (pd-1), programmed death-ligand 1 (pd-l1), and ebv-encoded rna (eber) expression in hodgkin lymphoma. *Ann. Hematol.* **2015**, *94*, 1545–1552. [CrossRef] [PubMed]
160. Kis, L.L.; Salamon, D.; Persson, E.K.; Nagy, N.; Scheeren, F.A.; Spits, H.; Klein, G.; Klein, E. Il-21 imposes a type ii ebv gene expression on type iii and type i b cells by the repression of c- and activation of lmp-1-promoter. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 872–877. [CrossRef] [PubMed]
161. Kis, L.L.; Gerasimcik, N.; Salamon, D.; Persson, E.K.; Nagy, N.; Klein, G.; Severinson, E.; Klein, E. Stat6 signaling pathway activated by the cytokines il-4 and il-13 induces expression of the epstein-barr virus-encoded protein lmp-1 in absence of ebna-2: Implications for the type ii ebv latent gene expression in hodgkin lymphoma. *Blood* **2011**, *117*, 165–174. [CrossRef] [PubMed]
162. Merchant, M.; Swart, R.; Katzman, R.B.; Ikeda, M.; Ikeda, A.; Longnecker, R.; Dykstra, M.L.; Pierce, S.K. The effects of the epstein-barr virus latent membrane protein 2a on b cell function. *Int. Rev. Immunol.* **2001**, *20*, 805–835. [CrossRef] [PubMed]
163. Fukuda, M.; Longnecker, R. Epstein-barr virus latent membrane protein 2a mediates transformation through constitutive activation of the ras/pi3-k/akt pathway. *J. Virol.* **2007**, *81*, 9299–9306. [CrossRef] [PubMed]
164. Mancao, C.; Altmann, M.; Jungnickel, B.; Hammerschmidt, W. Rescue of "crippled" germinal center b cells from apoptosis by epstein-barr virus. *Blood* **2005**, *106*, 4339–4344. [CrossRef] [PubMed]
165. Chaganti, S.; Bell Ai, A.I.; Pastor, N.B.; Milner, A.E.; Drayson, M.; Gordon, J.; Rickinson, A.B. Epstein-barr virus infection in vitro can rescue germinal center b cells with inactivated immunoglobulin genes. *Blood* **2005**, *106*, 4249–4252. [CrossRef] [PubMed]
166. Bechtel, D.; Kurth, J.; Unkel, C.; Küppers, R. Transformation of bcr-deficient germinal-center b cells bybv supports a major role of the virus in the pathogenesis of hodgkin and posttransplantation lymphomas. *Blood* **2005**, *106*, 4345–4350. [CrossRef] [PubMed]
167. Mancao, C.; Hammerschmidt, W. Epstein-barr virus latent membrane protein 2a is a b-cell receptor mimic and essential for b-cell survival. *Blood* **2007**, *110*, 3715–3721. [CrossRef] [PubMed]
168. Vockerodt, M.; Wei, W.; Nagy, E.; Prouzova, Z.; Schrader, A.; Kube, D.; Rowe, M.; Woodman, C.B.; Murray, P.G. Suppression of the lmp2a target gene, egr-1, protects hodgkin's lymphoma cells from entry to the ebv lytic cycle. *J. Pathol.* **2013**, *230*, 399–409. [CrossRef] [PubMed]
169. Portis, T.; Longnecker, R. Epstein-barr virus (ebv) lmp2a alters normal transcriptional regulation following b-cell receptor activation. *Virology* **2004**, *318*, 524–533. [CrossRef] [PubMed]

170. Portis, T.; Dyck, P.; Longnecker, R. Epstein-barr virus (ebv) lmp2a induces alterations in gene transcription similar to those observed in reed-sternberg cells of hodgkin lymphoma. *Blood* **2003**, *102*, 4166–4178. [CrossRef] [PubMed]
171. Portis, T.; Longnecker, R. Epstein-barr virus lmp2a interferes with global transcription factor regulation when expressed during b-lymphocyte development. *J. Virol.* **2003**, *77*, 105–114. [CrossRef] [PubMed]
172. Anderson, L.J.; Longnecker, R. Epstein-barr virus latent membrane protein 2a exploits notch1 to alter b-cell identity in vivo. *Blood* **2009**, *113*, 108–116. [CrossRef] [PubMed]
173. Chang, R.A.; Miller, S.D.; Longnecker, R. Epstein-barr virus latent membrane protein 2a exacerbates experimental autoimmune encephalomyelitis and enhances antigen presentation function. *Sci. Rep.* **2012**, *2*, 353. [CrossRef] [PubMed]
174. Kulwichit, W.; Edwards, R.H.; Davenport, E.M.; Baskar, J.F.; Godfrey, V.; Raab-Traub, N. Expression of the epstein-barr virus latent membrane protein 1 induces b cell lymphoma in transgenic mice. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 11963–11968. [CrossRef] [PubMed]
175. Zhang, B.; Kracker, S.; Yasuda, T.; Casola, S.; Vanneman, M.; Homig-Holzel, C.; Wang, Z.; Derudder, E.; Li, S.; Chakraborty, T.; et al. Immune surveillance and therapy of lymphomas driven by epstein-barr virus protein lmp1 in a mouse model. *Cell* **2012**, *148*, 739–751. [CrossRef] [PubMed]
176. Vrazo, A.C.; Chauchard, M.; Raab-Traub, N.; Longnecker, R. Epstein-barr virus lmp2a reduces hyperactivation induced by lmp1 to restore normal b cell phenotype in transgenic mice. *PLoS Pathog.* **2012**, *8*, e1002662. [CrossRef] [PubMed]
177. Ma, S.D.; Tsai, M.H.; Romero-Masters, J.C.; Ranheim, E.A.; Huebner, S.M.; Bristol, J.; Delecluse, H.J.; Kenney, S.C. Lmp1 and lmp2a collaborate to promote epstein-barr virus (ebv)-induced b cell lymphomas in a cord blood-humanized mouse model but are not essential. *J. Virol.* **2017**. [CrossRef] [PubMed]
178. Minamitani, T.; Ma, Y.; Zhou, H.; Kida, H.; Tsai, C.Y.; Obana, M.; Okuzaki, D.; Fujio, Y.; Kumanogoh, A.; Zhao, B.; et al. Mouse model of epstein-barr virus lmp1- and lmp2a-driven germinal center b-cell lymphoproliferative disease. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 4751–4756. [CrossRef] [PubMed]

© 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).