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Review Article

Sarcomas in Association with Human Herpesviral Infection

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Abstract

In the recent years, two lymphotropic gamma herpesvirus, HHV8 and EBV have been identified as the causative agents of lymphoproliferative disorders and lymphomas, in complication with immunocompromised status due to the infection Human Immunodeficient Virus (HIV) or immune suppressing therapy after organ transplant. Some of the transforming and proliferation promoting genomic products coded by the two herpeviruses causes malignant transformation of the lymphocytes similar with the immortalization process to convert B cells into lymphoblastoid cell lines in culture. The two herpesviruses are associated with other malignancies than hematopoietic tumors. EBV and HHV 8 play a pathogenic role in the genesis of Kaposi's sarcoma and leiomyesarcoma, respectively. This suggests that in immune deficient persons, opportunistic tumors other than lymphomas can be caused by the lymphotropic herpesviruses.

Keywords: Herpesvirus; Human herpesvirus type 8 (HHV 8); Epstein-Barr virus(EBV); Acquired immune deficiency syndrome (AIDS); Lymphoproliferative disorder; Lymphoma; Post-transplant lymphoproliferative disorder (PTLD); Kaposi's Sarcoma; Leiomyosarcoma

Abbreviations

HHV-8: Human Herpesvirus type 8; KSHV: Karposi's Sarcoma associated Herpesvirus; PEL: Pleural Effusion Lymphoma; Rta: Regulator of Transcriptional Activation or Replication and transcription activator; EBER: Epstein-Barr virus Encoded small RNA; EBNA: Epstein-Barr virus determined Nuclear Antigen; PTLD: Post-Transplant Lymphoproliferative Disorder

Introduction

To date, at least two human sarcomas have been identified to be associated with infection of lymphotropic herpesviruses, and they mostly occur in complication with immune compromise. The two sarcomas are Kaposi's sarcoma and leiomyosarcoma.

Two major lymphotropic human gamma-herpesviruses, Kaposi's Sarcoma Associated Herpesvirus (KSHV) or Human Herpesvirus Type 8 (HHV-8), and Epstein Barr virus (EBV) or HHV-4 cause lymphoproliferative disorders and sarcomas in immunocompromise hosts. The genesis of lymphomas may be attributed to the up-regulation the viral genomic expression. In AIDS patients, the secondary lymphomas are Body Cavity Based Lymphoma (BCBL) and Primary Effusion Lymphoma (PEL), together with Multicentric Castleman Disease (MCD) [1]. EBV is the pathogen of the lymphomas in post-transplantation with reduced antiviral immunity, the compromised condition is also caused by infection of HIV. In immunocompromised individuals, infection of the two viruses is also associated with two distinctive types of sarcoma, Kaposi's sarcoma, and leiomyosarcoma.

HHV-8 and Kaposi's sarcoma

Background: In 1994, Yuan Chang and collaborators identified a unique sequence present in more than 90 per cent of Kaposi's Sarcoma (KS) obtained from patients with AIDS The sequence was not present in tissue DNA from non-AIDS patients, but also present in 15 % of non-KS tissue DNA sample from AIDS patients. The homologs of capsid and tegument protein genes of Gammaherpesvirinae, herpesvirus saimiri, and Epstein Barr virus (EBV) were found in the sequences, and it defines a new human herpesvirus [2].

Until the time of the discovery of the human herpesvirus, termed Kaposi's Sarcoma Associated Herpesvirus (KSHV), or Human Herpesvirus Type 8 (HHV-8), seven human herpesviruses have been isolated, and they were classified as subgroups alpha, beta and gamma, with different spectrum of pathogenesis in the human hosts. Human cytomegalovirus, known as HHV-5 is fallen into the subgroup beta (the members are called beta-herpesviruses) together with HHV-6 and HHV-7. HHV-6 is further classified as variants HHV-6A and -6B, according to the genomic variation [3]. But the existence of variant for HHV-7 was not evidenced [4]. The two viruses are characteristically T cell tropic and associated with a rash, *exanthem subitum* [5].

Two gamma-herpesviruses, HHV-8 and EBV or HHV-4, manifest lymphotropism and they could establish persistent latency in host cells, their transforming genomic products engage multiple intracellular pathways signaling proliferation stimulation, prone to malignancy.

In the case of HHV-8, the oncogenic genomic products also transform vascular endothelial cells in a less well defined mechanism, leading to a malignancy at the infection size called Kaposi's sarcoma.

Genomic products with pathogenic potential

KSHV/HHV8 genome contains 90 Open Reading Frames (OFRs)

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[6], include functional proteins which modulates cell activities, to prolong the life span, support growth and proliferation and inhibit apoptosis, as so to facilitate the viral replication. The ORF K 50 within the genome of HHV-8 also codes for a protein which plays a role in the switch from latent to lytic replication. In vicinity of the OFR12 coding for kaposin family, the transcripts of 12 HHV-8 microRNAs are generated. The alignment of the ORFs of HHV-8 genome is referred to Figure 1.

HHV-8 replication and transcription activator (Rta): On entering a permissive cell and establishing infection, HHV-8 adopts latent and lytic replication. During latent infection, the virus maintains in nucleus as minichromosomes or integrates in the host chromosome and expresses latent gene products. Some of these products expressed by HHV-8 plays a role in the modulation of cell growth and proliferation, and hence contributes to the malignant transformation of HHV-8 harboring cells [8-12]. Like all herpesviruses, the latency can switch to lytic replication, when triggering by certain environmental factors like 2-tetradecanoyl-phoborl-13-acetate (TPA). When the virus enters lytic cycle of replication, viral DNA is massively amplified, and progenitor virions are produced, and viral particles are released on the rupture and death of the infected cells. Some herpesviral proteins are responsible for the latent-lytic program switch. Regulator of Transcription Activation (Rta) molecules are expressed by EBV and HHV-8. The EBV encoded Rta, also called ZEBRA is the product of BZLF1 gene, and HHV-8 Rta is generated by ORF50, whose expression is sufficient for the reactivation of HHV-8 [13,14], Rta transactivates the viral genes associated with lytic replication of cytokine production, together with its own promoter [15,16]. And it is required for the initiation of lytic DNA replication [17].

Latent proteins coded by viral genome: The genomic products expressed by HHV-8 virus have strikingly characteristics in mimicry or piracy of the human protein activities because its genome encodes for a number of homologs of biologically active cellular protein. The proteins include viral homolog of the angiogenic cytokine interleukin-6 (vLI-6), viral interferon regulatory factor 3 (vIRF3), a pro-survival protein which interferes interferon, an NF-kappaB activating viral FLICE/caspase-8 inhibitory protein (vFLIP), G1-S cell cycle promoter viral cyclin (v-cyclin), together with Latent Associated Nuclear Antigen (LANA), and Latency Associated Membrane Protein (LAMP), mitogenic signaling membrane protein, The proteins potentially support the proliferation of the host cells

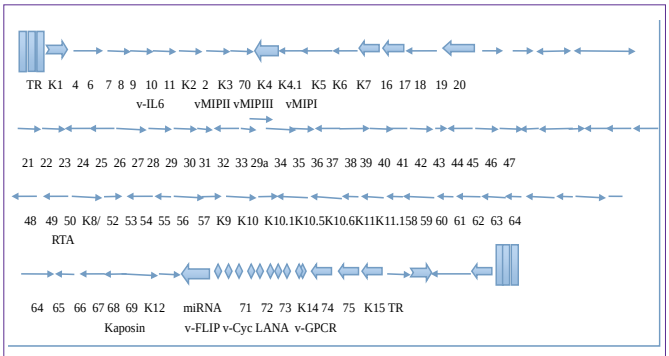

Figure 1: Scheme of HHV-8 genome encoding genes (adapted from [7]; The arrows represent the known products coded by genome of HHV-8).

by promoting cell cycle progression and other relevant events. The genomic products are discussed in the order of the alignment of coding ORFs.

v-IL-6 and MIP-1 proteins encoded by ORF K2: A homolog of mammalian interleukin-6 (IL-6) and two homologues of macrophage inflammatory protein MIP-1 was identified in this locus [18]. The HHV-8 encoded IL-6 shares functional properties with human IL-6 proteins. And it is expressed during both latent and lytic replication. The v-IL6 is speculated to be implicated in the genesis of Kaposi's sarcoma via angiogenic activity, and MIP-1 proteins may enhance pathogenic effects through the chemotactic recruitment of endogenous cytokine-producing cells into affected tissues. V-IL-6 is involved not only in the pathogenesis of Kaposi's sarcoma but also in certain B-cell lymphomas and multicentric Castleman's disease. It has conserved important features such as cysteine residues involved in disulfide bridging or an amino-terminal signal peptide. Most notably, the region involved in receptor binding is highly conserved in vIL-6 [19].

vIRF: Viral Interferon Regulatory Factor (vIRF) is encoded by ORF K9 in HHV-8 genome [20]. Antiviral response is initiated and amplified by interferon (IFN) induced by viral infection. The pleiotropic activity of IFNs includes tumor suppression through induction of negative cell growth regulator, and induction of apoptosis. vIRF coded by HHV-8 bears sequence similarity with IRF proteins, and all such proteins positively or negatively regulates IFN signaling. It has been reported that vIRF inhibits IFN signal transduction, downregulates Cyclin-Dependent Kinase (CDK) inhibitor p21, and transforms NIH3T3 cells [21].

LANA-2: The protein latency associated nuclear antigen 2 (LANA 2) is encoded by ORFK 10.5. Its expression is B cell specific and not present in Kaposi's sarcoma tissue. The coding genes ORF K9 and K10.5 appear to arise through gene duplication of a captured cellular IRF gene. LANA 2 is potent inhibitor of p53-induced transcription, and antagonizes p53-induced apoptosis [22].

Kaposin, encoded by ORF K12: Kaposin is a type II membrane protein. Its abundance and ability to transform cells, suggests its potential role in KS pathogenesis [23]. kaposin expressing construct induced focal transformation in Rat3 cells when transfected to the cells. All the cells produced high-grade, highly vascular, undifferentiated sarcomas upon subcutaneous injection of athymic nu/nu mice [24].

V-FLIP: Encoded by K13, was initially thought to be an inhibitor of caspase-8 and because of its sequence homology to the prodomain of caspase 8/FLICE, and it was classified as viral FLICE inhibitory protein (vFLIP) [10]. But the subsequent work revealed that the K13 protein does not act as a vFLIP and instead interact with IkappaB kinase (IKK) complex and activates the NFkappaB pathway [25,26]. Its transforming ability was demonstrated [23]. It was reported that K13/Myc double transgenic mice developed lymphoma in shorter latentcy, and the development of lymphoma in the mice was associated with elevated K13 level, and enhanced NFkappaB activity, and decrease in apoptosis [27].

v-GPCR: The coding product of ORF K14 is the most important intracellular signaling molecule that induces gene expression [28-31]. The viral G protein coupled receptor (v-GPCR) is the distant relative

of the IL-8 receptor, and displays a strong signaling activity in the absence of any known ligand, and considered to be constitutively active [28]. V-GPCR is expressed during the mid-lytic cycle, and the downstream gene of a biscitronic mRNA [31]. Its ectopic expression triggers growth deregulation in fibroblasts [30].

v-cyclin D: Is the coding product of ORF 72, and is transcribed from the same promoter element as LANA encoded by ORF73 [31]. Structurally, it is similar with the cellular D-type cyclins. It also associates with cellular Cyclin Dependent Kinase-6 (CDK-6) to form an active kinase complex. The kinase complex phosphorylates tumopr suppressor pRB as well as p27 KIP1, p21CIP1, and Bcl-2 [32,33]. The complex may lead to a deregulated cell cycle progression and transformation [34,35].

LANA-1: Translational product of ORF 73. The viral protein is regarded as the functional homolog of Epstein-Barr virus determined nuclear protein 1 (EBNA-1), as it plays an essential role of maintenance of the viral episome in the infected cells. A strikingly difference of LANA-1 from EBNA-1 is that it also possesses transformation associated ability, some functions even resemble what exerted by transforming proteins of EBV like Latent Membrane Protein 1 (LMP1). It has been shown that LANA-1 associates with several cancer related proteins like Rb [11], p53 [12], and RING3 [36].

v-Bcl-2: known as KSbcl-2 was identified in the HHV-8 genome at an equivalent position and orientation to that of ORF16 in Herpesvirus Simplex (HVS). The overall amino acid sequence identity between KSbcl-2 and other Bcl-2 homologs is low (15-20%) but concentrated within the BH1 and BH2 regions. Its over-expression blocked apoptosis as efficiently as the known cellular anti-apoptptic Bcl-2 proteins. But it does not homodimerizes nor heterodimerizes with other Bcl-2 family members, suggesting that KSbcl-2 may have evolved to escape any negative regulatory effects of the cellular Bax and Bak proteins [37].

The progress on the characterization of the properties and biological activities of these proteins has provided insight into the potential mechanisms of HHV-8-induced neoplasia, including lymphoproliferative disorders, lymphomas, and Kaposi's sarcoma. A combination of cell transformation mediated by latently expressed proteins that promote cell proliferation and survival coupled with paracrine signaling functions mediated by either the viral cytokines or viral receptor-induced secreted cellular proteins triggers the events leading to malignancy genesis.

MicroRNAs encoded by HHV-8 genome: MicroRNA (miRNA) is a class of single strnaded small RNA of 22 nucleotide, which is matured from a large primary transcript, and a stem-loop pre-miRNA [38,39]. Regulation of the biological events during the life cycle by the small RNA constitutes a great advantage for the parasitic viruses, because they do not elicit antiviral immune response like the viral proteins [40]. miRNAs are known to expressed by different viruses. EBER1 and ERBER2 encoded by EBV genome without any translational products were the earliest viral miRNA identified even before the notion of miRNA was proposed [41,42]. They are expressed abundantly in all EBV infected cells serving as indicator of EBV infection. HHV-8 encodes 12 miRNA [43-46]. The coding genes are clustered in vicinity of ORF K12 coding for kaposin family protein. They reside in the intron or coding region of large kaposin transcript, and target to certain cellular components. It has been shown that cell expressing HHV-8 miRNA are less sensitive to apoptosis induced by caspase-dependent and independent apoptosis induced by genotoxins [47]. HHV-8 encoding miR-K12-1, 3, and -4-3p regulate the activity of caspase-3, the effector of intrinsic and extrinsic apoptosis. Reports also suggested that HHV-8 encoding miRNAs regulate the maintenance of viral latency and inhibit lytic replication [48].

Viral association of the lymphoproliferative disorders

Primary Effusion Lymphoma (PEL) is a characteristic malignancy occurring in AIDS patients. The malignant cells are present in effusion of body cavities like peritoneal, pleural or cardial spaces without an obvious tumor mass. The lymphomatous cells have pleomorphic or anaplastic features. Most cases are of B cell origin, as indicated by the rearranged immunoglobulin locus or monotypic light chain pattern [49]. T cell type, HHV-8 associated PEL has been reported, with the diagnosis on basis of clonal rearrangement of T cell receptor perptide chain gene [50,51].

HHV-8 association of Kaposi's sarcoma

Kaposi's sarcoma was first described by a Hungarian dermatologist Moritz Kaposi in 1872, as a "idiopathic multiple pigmented sarcoma of the skin" [52,53]. The type or variant originally documented, known as classical variant today, is a relatively rare, slow-growing malignancy, mostly seen in middle-aged or elderly men. In 1981, a new variant which was eventually proved to be HIV associated form of Kaposi's sarcoma was reported by Alvin Friedman-Kein [54]. HHV-8 infection in this type of Kaposi sarcoma was demonstrated in 1994 and the pathogenic role of the lymphotropic herpesvirus has been intensively studied, in connection with the biological activities of the viral genomic products in the subsequent years. Almost all the reported in the United States and other countries have occurred in homosexual and bisexual men [55], the epidemic or HHV-8 associated Kaposi's sarcoma which tends to disseminate widely to mucous membranes and viscera is regarded as the most common neoplastic complication of AIDS. The third form of Kaposi's sarcoma is immunosuppression associated. This type occurs in patients of organ transplant who received immune suppression therapy. Immune deficiency caused both HIV infection or iatrogenic immune suppression suggests Kaposi's sarcoma an opportunity tumor attributed to imunocompromised status. The last type of KS is endemic, which is prevalent in some part of Africa. Kaposi's sarcoma occurs in these patients with the fore-running AIDS episode.

EBV and Leiomyosarcoma

Background

EBV has been shown to be the pathogen of a variety of human diseases. Biologically, it is distinctively characteristic with a host cell dependent latency pattern. In lymphomas arising in immunocompromised individuals, notably those occurring secondary to AIDS, it is evidenced that EBV may play a role. And the viral genome and/or genomic products have been detected in a considerable of the cases, including 80% of the central nervous system lymphoma [56], 70% immunoblastic lymphoma [57]. Major proteins with transforming potential are expressed, and the immunodominant

and also transforming viral proteins are expressed only in the host with reduced immunity. EBV encoding nuclear antigen, EBNA2, and Latent Membrane Protein 1(LMP1) which is transactivated by EBNA2 in the microenvironment of B cells play an essential role in the EBV mediated malignant transformation to convert the target cells into lymphoblastoid phenotype. The immortalized lymphocytes form large clumps due to the up-regulation of the adhesion molecules like Intercellular Adhesion Molecule1 (ICAM1), and CD23, LFA3 [58,59] and anti-apoptotic molecules bcl-2 [58], mcl-1[60], and zinc finger A20 [61]. Other malignant related genes induced by EBV encoding genes, like Id1 (inhibitor of differentiation 1) [62] may also contribute to the genesis of tumors other than lymphoma, like meiomyosarcoma.

In two neoplasms of epithelial origin, Nasopharyngeal Carcinoma (NPC) and EBV-associated gastric cancer, latency types with downregulated genomic expression are adopted. Transforming proteins, LMP1, LMP2A and 2B are expresed in NPC, and they engage intracellular signal pathways [63-66]. Recently, it has been shown that EBV acts as a regulator of genetic or epigenetic events rather than directly transforming effector in gastric cancer [67-70]. The latency pattern of EBV in leiomyosarcoma remains to be characterized, so as to understand the role of EBV in its genesis.

The association of EBV infection with human malignancies prompts its utility as a therapeutic target. OriP as a viral regulatory element, for example, drives the expression of EBV encoding genes, it could be manipulated to control the expression of tumor suppressor genes and other cytotoxic factors, to achieve bitotherpeutical goal in EBV associated tumors [71].

EBV Genomic products with pathogenic potential

Zta/ZEBRA and latency/lytic cycle switch of EBV: Upon entry of EBV to the host B lymphocytes, the infected cells rapidly expand, analogous to the EBV immortalization of cultured B cells into Lymphoblastoid Cell Lines (LCLs). Lifelong EBV latency is established following an EBV specific Cytotoxic T Lymphcyte (CTL) response [72].

Like all herpesviruses, EBV adopts two distinctive forms of infection, latency and lytic replication. The activation of lytic cycle is evidenced by the presence of the virions in throat washing of healthy carriers, and plays an essential role in expansion of the EBV infected B cell compartment. It has been known that two intermediate early viral proteins, Zta/ ZEBRA, coded by BZLF1 ORF and replication and transcription activator (Rta) coded by BRLF1 are responsible for the switch from latent to lytic form of replication [73,74]. Zta and Rta are silenced during latent infection of EBV, but are activated by external stimuli like TPA [75,76] and a cascade of intracellular signal transduction is triggered [77,78].

Zta/ZEBRA which plays a role in switch to lytic cycle has been intensively studied. It is a DNA binding protein related to the basic(b) ZIP family of transcription factors which transactivates early, lytic-phase viral promoter via Zta Responsive Element (ZRE) motif [79]. Zta protein contains a carboxyl-terminal domain that mediates homodimerization through a coiled-coil interaction, and a basic region which shares sequence homology with the DNA binding domain of members of AP-1 family of transcription factors [80-82]. It can therefore binds to TPA-responsive element or AP-1 sequence motifs with high affinity [83,84].

Two viral molecules, Zta and Rta have been shown to be indispensable for the induction of lytic cycle entry. But in view of that the process is completed by two factors, it raises the question whether one protein is sufficient in the switch. Recombinant EBV, like mini-EBV has been constructed to study the effect of individual gene product on cells [85]. LCL harboring such EBV with intact genome termed 2089, and that with deletion of BZLF1 ORF, 2809 were co-cultivated with target epithelial cells. HONE-1 cells derived from nasopharyngeal carcinoma were infected with the two strains of recombinant EBV. We have found that BZLF1 mutant strain of EBV also possessed the ability to infect the target cells (Figure 2). The precise mechanism for the maintenance of the infectability of the BZLF1 deleted viral strain remains to be elucidated.

The role of genomic products expressed during viral latency in malignancy transformation mediated by EBV

EBV adopts different types of latency in different host ranges. In immune deficient individuals, all the genomic products, 6 nuclear proteins, EBNA 1-6 and three membrane integral proteins, latent membrane proteins 1 (LMP1), 2A (LMP2A) and 2B (LMP2B) are expressed. EBNA1 is a nuclear protein that maintains viral episomal status. It is expressed in all cells infected EBV.

EBNA 1, with a molecular weight ranging from 90-110 kDa, depending on strain origin, is non-immunogenic. The property is attributed to the presence of a unique sequence, Gly-Ala repeat on its amino-terminus, which prevent the ligase catalytic ubiquitination, and thus it is unable to be cleaved to form epitopes by Antigen Processing Cells (APC) [86]. In the endemic region of nasopharyngeal carcinoma, a human cancer tightly associated with EBV infection, three EBNA1 subtypes, P-ala, V-thr and V-val have been detected from healthy carriers. Their effect on cell proliferation was examined. And V-val-EBNA1 was statistically higher than P-ala-EBNA1 in term

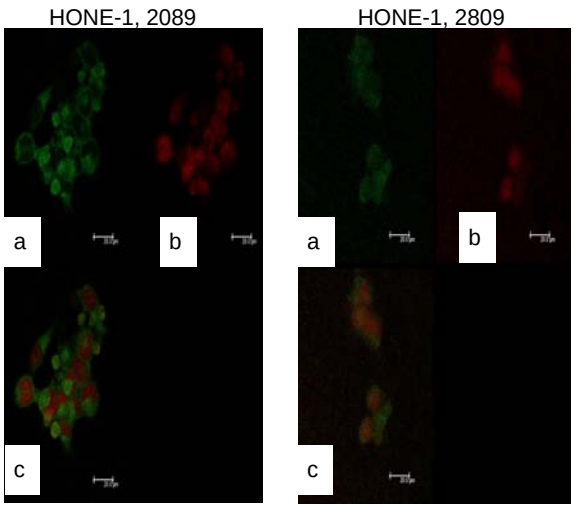

Figure 2: Infection of NPC derived HONE-I cells with LCL harboring wt recombinant EBV2089 (left) and mutant recombinant EBV with deletion of BZLF1, 2809(right) [85]. A. EGFP tag on virions; B. Nuclear counter stain with Propidium Iodide (PI); C. merge of EGFP and PI signals. Data derived from at least two independent tests.

of proliferation promotion. The type of EBNA1 with the functional advantage compared with prototype has been suggested [87].

EBNA2: EBNA 2-6 has been known as transforming viral protein, and in the recent years, publications have described their engagement in the intracellular pathways to stimulate growth and proliferation. Together with EBNA-5 or EBNA LP, it is the earliest expressed viral protein when B cells are infected with EBV [88]. Efficient immortalization of B lymphocytes requires the expression of genes of latency III program, including EBNA-2, which transactivates a number of viral proteins like oncogenic latent membrane protein 1 (LMP1), LMP2, and induces a set of cellular genes, notably c-myc [89,90]. Transcription activation of EBNA2 is exerted by its association with a transcription factor, CBF1 (C promoter binding factor 1), and the transformation potential of EBNA-2 is mediated by the complex formation. CBF1 is also targeted by the intracellular domain of a protein Notch, formed on proteolytical cleavage. Notch proteins are a group of highly species conserved, membrane bound protein. Its structure suggests of the role in multistage animal development [91-94]. It has been shown that both Notch and EBNA-2activates a important subset of cellular genes associated with type III latency and B cell growth, while EBNA-2 more efficiently induces important viral genes, like LMP-1 coding BNLF1 [95]. The exploitation of Notch-related signaling pathway may represent a key mechanism by which EBNA-2 contributes to EBV-induced cell immortalization.

EBNA 3: Termed EBNA3A in an alternative nomenclature system. Similar with EBNA-2, and the oncogenic membrane integral protein LMP1, EBNA3 proteins, EBNA-3 and EBNA-6 are essential for transformation of B cells into Lymphoblastoid Cell Line (LCL) [96,97]. EBNA3 acts as cell cycle regulator, and also as transcription repressor in EBV infected cells with type III latency. A negative cell cycle regulator, p16 INK4A is epigenetically repressed by EBNA 3, cooperating with EBNA 6, hence facilitates the outgrowing of LCL. In the context, the senescence or Rb mediated cell cycle arrest is inhibited. Also similar with EBNA-2, EBNA-3 and -6 bind CBF1, and inhibit the EBV genes activation by EBNA-2. In addition, the repressive activity of EBNA proteins is exerted by they directly target to DNA. They interact with cellular factors like HDAC, and CtBP (c terminal binding protein) [99-101].

EBNA4: Termed EBNA 3B. Masucci and collaborators have shown that population with high level of HLA locus A11 evade recognition by CTL specific for an immunodominant A11 restricted epitope derived from EBNA4 [102]. EBNA-4 coded by EBV as a human herpesvirus is less studied, and our knowledge mostly derived from the work on the rhesus lymphocryptovirus from a primate rhesus macaque. The EBNA 3 proteins, EBNA-3, 4 and 6 are expressed in immortalized B cells, and they may function as transcription regulators. Among these proteins, EBNA-3 and 6 are essential for cell immortalization, but EBNA-4 seems to be indispensable. In LCL with EBNA-4 null virus, a chemokine CXCR4 is upregulated, the result suggests that EBNA-4 regulation of CXCR 4 may be a viral strategy for alteration of B cell homing in the infected host [103].

EBNA6: Alternatively termed EBNA3C EBNA-6 exerts transcription repression in collaboration with EBNA-3, through binding of the factor HDAC and CtBP [99-101]. EBNA 6 functions as a transcription regulator, and reports showed that it regulates cell cycle progression, as an oncoprotein which directs cell cycle progression through the G1 phase restriction point when conditions might signal arrest. And it is functionally but not necessarily mechanistically, similar to the pRb-neutralizing nuclear antigens encoded by the 'small' DNA tumor viruses. EBNA-6 can cooperate with activated (Ha-)ras in co-transfection assays to immortalize and transform Rat Embryo Fibroblasts (REFs). EBNA3C also augmented transformation by (Ha-)ras and a mutant p53 to a similar extent as human papilloma virus E7. As with E7 this effect was not inhibited by cotransfection with the Cyclin-Dependent Kinase Inhibitor (CDKI), a p16INK4A, which can normally activate the retinoblastoma protein (pRb) and induce growth arrest. Also like E7/ras and E1A/ras transformed cells the EBNA3C/ras transformants are very susceptible to apoptotic cell death [104]. It has also been shown that EBNA-6 binds to a MRPS18-2 protein, and targets it to the nucleus. MRPS18-2 binds to both hypo- and hyperphosphorylated forms of Rb protein specifically. This binding targets the small pocket of pRb, which is a site of interaction with E2F1. EBNA-6 may play a major role in the entry of EBV infected B cells into the S phase by binding to and raising the level of nuclear MRPS18-2, protein [105].

EBNA5: Alternatively called EBNA Leader Protein (LP). A number of cellular proteins have been discovered to bind EBNA 5. EBNA 5 is one of the earliest viral proteins expressed on infection of B cells by EBV. A nucleolar protein p14 ARF which regulates the p53 pathway is associated with EBNA 5. EBNA 5 also binds a partly nucleolar located protein, the v-fos transformation effector Fte-1 (Fte-1/S3a), Fte-1/S3a has multiple biological functions. It enhances v-fos-mediated cellular transformation and is part of the small ribosomal subunit. It also interacts with the transcriptional factor CHOP and poly(ADP-ribose) polymerase (PARP) which is cleaved by pro-apoptotic protease when host cells undergoing apoptosis [106]. Fte-1/S3a is regularly expressed at high levels in both tumors and cancer cell lines. Its high expression favors the maintenance of malignant phenotype and undifferentiated state, whereas its down-regulation is associated with cellular differentiation and growth arrest. EBV-induced B cell transformation leads to the up-regulation of Fte-1/S3a. And the binding of EBNA-5 may influence the growth promoting, differentiation inhibiting, or apoptosis regulating functions of Fte-1/S3a [107].

Latent membrane proteins (LMPs): The proteins include LMP1 coded by fragment BNLF1 on the viral genome, and LMP2A and 2B coded by BNLF2. LMP1 is membrane integral with six transmembrane loops. It has a short N-terminal tail, but a C-terminal tail of more than 200 amino acid residues, harboring two Transformation Effector Sites (TESs). Both membrane proximal and distal TESs are capable of inducing NFkappaB, the hallmark of the biological activity of LMP1 [108] and the distal site also engages JNK, JAK/STAT, and Akt pathways. The association of TRAFs and TRADD defines LMP1 as a member of Tumor Necrosis Factor Receptor Superfamily (TNFRSF) [109,110]. LMP1 is recognized as a homolog of eukaryotic CD40, aggregated to form dimer on cells surface, without the triggering of an extracellular ligand, constantly transducing growth signaling for the host cell [111]. A panel of proliferation supporting, anti-apoptotic molecular are induced by LMP1 in an NFkappaB dependent manner, including bcl-2, bfl-1, mcl-1, and A20 [58-61]. LMP2A is a homolog of B cell receptor. It is membrane integral, and contains 12

transmembrane loops. LMP2A persistently emits growth signal for B cells.

EBV association of the lymphoproliferative disorders

It is well known that EBV infection is associated with endemic Burkitt Lymphoma (BL), occurring primarily in individuals at childhood or early adolescence. Here we emphasize with the opportunistic lymphomas arising in immune deficient patients.

AIDS-associated immunoblastic and primary central nervous system lymphomas: As lymphomas arising in AIDS patients, immunoblastic and Primary Nervous System (PNS) lymphomas are immunoblastic or large cell type, histophatologically intermediate or high grade [56,57]. The lesions are extra-nodal and unusual, and the type of lymphoma is characteristic of rapid progressing. EBV genome, present as monoclonal is detected in 90% primary central nervous system and 70% immunoblastic lymphomas in complication with AIDS.

Post-transplant lymphoproliferative disorder/lymphoma: The type of disease occurs in patients with iatrogenic immune suppression due to administration of immunity inhibiting drugs after organ transplantation. The post-transplant lymphoproiliferative disorder and lymphoma are distinguished from Non-Hodgkin's Lymphoma (NHL) in immune competent individuals by higher proportion of tumors with CNS presentation and by that the lymphoma is polyclonal immunophenotypically and genotypically. Genome of EBV is detectable from the clinical specimens, supporting the causative role of EBV. Monoclonal origin of the viral strain is revealed by study of molecular epidemiological study. More than 95% of the cases are positive for EBV genome and latent gene products [112].

The inability of the host immune system to control EBV infection may the driving force behind post-transplant lymphomagenesis. Persons without EBV infection prior to organ transplant have particular high risk of the lymphomas [113].

Mechanism and viral association of leiomyosarcoma

Leiomyosarcoma is a rare smooth muscle tumor occurring in uterus or gastrointestinal tract, accounting for 5-10% of all sarcomas. It is slightly more common in female. The cases in children are EBV associated, and these patients normally have iatrogenic, congenital, and AIDS-associated immunosuppression [114]. Its incidence is dramatically increased in immunocompromised children. EBV negative leiomeyosarcomas have been seen in women after renal transplantation, and immune competent individuals. McClain et al reported that in six HIV infected patients, five had leiomyosarcoma, and two had leimyoma. EBV genome existed in smooth muscle cells but not other cells in these patients. EBV receptor was strongly positive in these patients on immunostaining and the reactivity was elevated HIV positive patients [115].

Conclusion

Two lymphotropic human herpesviruses, KSHV/HHV-8 and EBV have been intensively investigated in the recent years in regard with their basic biology and pathogenic activity. The latest work on HHV-8 mostly focused on the modulation of intracellular events like growth, proliferation and malignant transformation by hijacking host molecular activity, for example coding for cell cycle regulators, and synthesis of microRNAs. In immunocompromised host, HHV-8 causes certain types of lymphoma, and a vascular proliferative disorder, Kaposi's sarcoma. EBV is a ubiquitous human herpesvirus, its seroprevalence is high in the population. The virus adopts different latency in the individuals and immunodominant, and transforming genomic products are expressed in persons with immune suppression caused by administration of immune inhibitors on organ transplant, and infection of HIV. Expression of the transforming proteins leads to the occurrence of different types of opportunistic lymphomas, and, through complicated molecular interactions, a rare tumor on smooth muscle, leiomyosarcoma.

Acknowledgment

The manuscript is dedicated to the 89th birthday of Professor George Klein, Karolinska Institutet, Stockholm, Sweden. Professor Klein was among the scientists who first investigated the association of viral infection and cancer, significantly contributing to our understanding of the molecular mechanism of Burkitt lymphoma. He is still active in his scientific career, engaging in efforts in elucidating the interactions of the malignant cells with their microenvironment, and the work by his group on EBV encoding proteins in the context of malignant transformation is described in the present paper. We are grateful to Dr. Reinhard Zeidler, Helmhotz Center, Munich, Germany for kindly providing us with the LCL harboring recombinant EBV. Our work mentioned herein is supported by grants from National Natural Scientific Foundation of China (NSFC)(No. 31170676), and Guangdong Provincial Medical Research Fund (A2014467).

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