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Mini-review

HIV, EBV and KSHV: Viral cooperation in the pathogenesis of human malignancies

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ABSTRACT

Malignancies associated with Epstein–Barr virus (EBV) and/or Kaposi's sarcoma human herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is frequently found in patients infected with HIV. Both these human gammaherpesviruses are known for their oncogenic properties, for the viral products that mimic or interfere with the functions of critical cellular proteins, and the ability to escape the immune responses. The introduction of the highly active anti-retroviral therapy (HAART) has significantly decreased the frequency of Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and primary central nervous system lymphoma (PCNSL); conversely, for some lymphomas the incidence diminished only slightly, as in Burkitt's lymphoma (BL), or had no significant variations, as Hodgkin's lymphoma (HL). These observations may indicate that HAART might have a direct impact on KSHV and EBV biology, that there is a reconstitution of the immune system in HIV-infected patients under HAART, or even that HAART perhaps has a detrimental impact in the pathogenic interactions between HIV, EBV and KSHV. The present review aim to evaluate and to discuss the data available for these hypotheses, in order to shed more light on the mechanisms for the cooperation among HIV-1, EBV and KSHV that may culminate in cell transformation and cancer development in humans.

1. Introduction

Malignancies in individuals infected by the Human Immunodeficiency Virus (HIV) are frequently associated with co-infection by the Epstein–Barr virus (EBV), and/or the Kaposi's sarcoma-associated herpesvirus (KSHV) [1]. EBV and KSHV, also known as human herpesvirus 4 (HHV-4) and Human Herpesvirus-8 (HHV-8), respectively, are two gammaherpesviruses with known oncogenic properties for humans [2]. In the HIV infection setting, EBV is found in neoplastic cells in most of the Hodgkin's lymphoma (HL) cases, as well as in some non-Hodgkin's lymphomas (NHL), including Burkitt's lymphoma (BL), Diffuse Large B-cell lymphoma (DLBCL) of immunoblastic-plasmacytoid type, plasmablastic lymphomas, primary central nervous system lymphoma (PCNSL) and primary effusion lymphoma (PEL) [3]. In the other hand, KSHV is conclusively associated with all cases of Kaposi's sarcoma (KS) [4], and PEL [5].

Individuals infected by HIV have a 60–200-fold and 8–10-fold higher relative risk to develop NHL and HL, respectively, compared to the HIV-negative population. The degree of impairment of the immune system was suggested to be related with the development of specific NHL in HIV-positive patients. For instance, individuals with normal or slightly decreased number of circulating T CD_4^+ lymphocytes have a higher risk of BL and centroblastic DLBCL, whist the risk of PEL and plasmablastic DLBCL is higher among patients with severe immunodeficiency [6]. The incidence of KS in individuals infected with HIV, on the other hand, is 20,000-fold higher than in general

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population, and 300-fold higher than in persons with any other type of immunosuppression [7]. It has been previously reported that individuals co-infected with KSHV and HIV-1 have an increase of 60% in the probability for developing KS, per year of post HIV-infection [8].

With the introduction of the highly active antiretroviral therapy (HAART), around 1990, there were changes in the frequency of cancers associated with the Acquired Immunodeficiency Syndrome (AIDS). Notably, it was noted a significantly decrease in KS and a small decrease in NHL cases; the frequency of PCNSL, though, had declined drastically [9–14].

As KS is consistently linked with KSHV, and some of the NHL are linked with EBV and/or KSHV, few hypotheses may be considered to explain the decrease in the incidence of these cancers in the post-HAART era (Fig. 1). First, HAART might have some direct impact on KSHV and EBV reactivation and replication, with reflections in their viral load. Second, because of the partial reconstitution of the immune system, HAART-treated HIV-positive patients might have a better control over primary infection (mostly for KSHV), as well as viral reactivation (for both KSHV and EBV). This would decrease the odds for long-term cell transformation by the oncogenic gammaherpesviruses, and improve the immunovigilance against virus-transformed cells. And third, as HAART decreases the HIV burden within the organism, it could result in a decreased interaction between HIV and KSHV and/or EBV, so that viral products that may cooperate for cell transformation will not. In the post-HAART era, the incidence of BL in HIV-treated patients was invariable or had increased slightly overtime [15,16], and there were no significant variations in the frequency of HL [15]. This data suggest lack of a direct negative impact of HAART in the EBV biology [17]. Although the drastic decrease in the incidence of Aids-associated KS might indicate that this could be the case for KSHV, it is also controverse whether some drugs included in the anti-retroviral therapy directly affect this gammaherpesvirus [18]. On the other hand, there is enough data indicating that HAART has a more unspecific effect stimulating the immune system [19–25], as presumed in the second hypothesis. Indeed, the importance of the immune system status in the pathogenesis of proliferative diseases and cancers associated with infection by EBV or KSHV may be even inferred outside the HIV setting. For instance, it is well established the association of EBV with the development of post-transplant lymphproliferative disease (PTLD) [26,27], and non-Aids-associated KS lesions also arises under some degree of immunosuppression (e.g., immunosenescence in classic KS) [28].

Conversely, this does not exclude that HAART may also have an indirect effect impairing the HIV and KSHV and/or EBV interaction in cancer pathogenesis. Noteworthy, viral cooperation would explain the higher aggressiveness of KS in HIV-infected people. The main scope of the present review is to explore possible mechanisms for viral cooperation in the context of human carcinogenesis; thus, elements for the third hypothesis previously mentioned will be discussed further. As diseases implicating HIV, EBV and KSHV will be used as models, interactions between those viruses will be considered in order to contribute for a better understanding on the etiopathogenesis of gammaherpesvirus-associated cancers in the HIV setting.

In the following sections, some background information about the biology of HIV-1, KSHV and EBV will be provided for better understanding of the known or putative interactions among these viruses for cell transformation and cancer development in humans.

2. HIV

The HIV genome includes the basic set of retroviral genes *gag*, *pol* and *env*. Whereas *gag* encodes structural (e.g., p24, p7 e p6) and matrix proteins (e.g., p17), *pol* encodes proteins required for HIV replication (the reverse transcriptase, integrase and protease enzymes), and *env* encodes the glycoproteins (e.g., gp120 and gp41) that interact with the molecules expressed on the surface of the target cells. Regulatory proteins are also encoded in the HIV genome, including the regulator of expression of the virion – rev, the transactivator of transcription – tat, and four accessories proteins: the negative factor – nef, the viral protein R – vpr, the viral protein U – vpu,

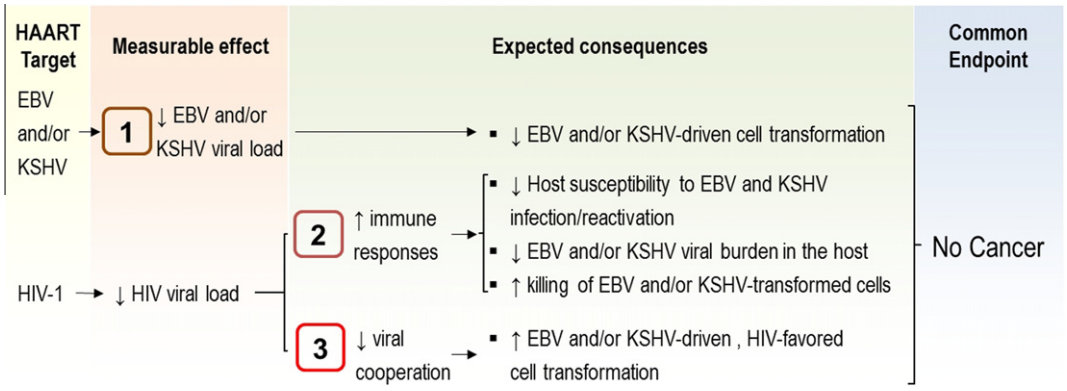

Fig. 1. Hypotheses to be considered to explain the impact of HAART in the development of EBV and KSHV-associated cancers. (1) HAART has a direct impact on KSHV and EBV reactivation and replication; (2) partial reconstitution of the immune responses against viral infection as a consequence of HAART; (3) HAART decreases the interaction between HIV and KSHV and/or EBV.

and the virus infectivity factor – vif [29]. The main targets for HIV infection are the CD_4-expressing subset of T lymphocytes and cells of monocytic/macrophagic lineage. The CD_4 molecule expressed in the cell surface is used by HIV as a primary receptor. However, successful cell entry relies also in the interaction between membrane-bound retroviral gp120 and the cellular CXCR4 or CCR5 molecules (α and β chemokines receptors), required as co-factors for gp41-mediated fusion of viral and target cell membranes.

With the introduction of the HIV-1 nucleocapsid in the cytoplasm, the retroviral RNA released is converted to a proviral DNA by the reverse transcriptase enzyme. The proviral DNA is transported to the nucleus and incorporated to the cellular genome by the retroviral integrase. The transcription initiation for the integrated provirus relies on the U3-R-U5 sequence in the HIV-1 long terminal repeat (LTR) via cellular RNA polymerase II. Though the U3-R-U5 is presented at both ends of the viral DNA, only the 5′ LTR is used for proviral transcription. The retroviral genomic RNA produced are categorized into three classes: unspliced RNA, which is exported to the cytoplasm to serve as mRNA for Gag and Gag-Pol synthesis, and to be included into the newly-produced viruses; partially splice mRNA, which encode env, vif, vpu and vpr proteins; and multiple-spliced RNAs, which encodes rev, tat and nef proteins. Soon after or throughout the virus release from the plasma membrane, the viral protease cleaves gag and gag-pol polyproteins, in order to generate gag and pol mature proteins that characterizes the infectious HIV-1 particles [30].

3. Human gammaherpesvirus

The human gammaherpesviruses (Order *Hespevirales*, family *Hespeviridae*, subfamily *Gammaherpesvirinae*) are currently subdivided into five genera, including the *Lymphocryptovirus* and *Rhadinovirus*, which EBV and KSHV belongs to, respectively [31]. The EBV and KSHV genomes are double-strand linear DNAs with approximately 170kpb, usually kept in the nucleus of the infected cells as circular episomes. The tropism for lymphocytes is one of the distinct features of gammaherpesviruses. Once infected, these cells are driven to sustained proliferation, and eventually immortalization and malignant transformation. Gammaherpesviruses also have the ability to establish a latent biologic cycle in infected cells, in which only a limited set of viral genes are expressed. As episomes, the viral genomes behave as a cellular chromosome, being replicated and segregated between daughter cells during the mitosis [32].

Lytic reactivation for all gammaherpesvirus is dependent on "switch proteins". In KSHV, the Replication and Transcription Activator protein (Rta; viral ORF50) is the main regulator for expression of lytic genes and viral replication. EBV, on the other hand, has two different proteins relevant for the same activities: its own Rta (viral BRLF1) and the EBV Zta (encoded by BZLF1) [33]. Regulation of lytic reactivation for EBV and KSHV relies also in cellular proteins, notably the NF-κB family of transcription factors [2,34].

During infection, EBV and KSHV actively hijack the infected host cell via expression of different viral products. Interestingly, some of these products have high degree of functional and/or structural homology with critical cellular proteins, which interferes in cell proliferation, apoptosis and modulates the immune responses. In this regard, representative examples are indicated in Table 1. Especially for KSHV, several of these viral homologs were implicated in viral-induced cell transformation [2,35].

Table 1
List of major KSHV and EBV homologs for cellular proteins with activity in cell proliferation, apoptosis and modulation of the immune responses.

Phenomenon	KSHV homolog	EBV homolog
Cell proliferation	vCyc (ORF72)	
Apoptosis	vbcl-2 (ORF16) vFLIP (ORF71/ ORFK13) vIAP (ORFK7)	BHRF-1 (BamHI fragment H rightward open reading frame-1)
Immune responses	vIL-6 (ORFK2) vIRF (ORFK9) vMIPI (ORFK6) vMIPII (ORFK4) vGPCR (ORF74) ORFK14	vIL10 (BCRF1)

vCyc – viral cyclin; vFLIP – viral FAS-associated death domain-like interleukin-1β converting enzyme (FLICE)-like inhibitory protein; vIAP – viral inhibitor-of-apoptosis protein; vIRF – interferon regulatory factor; vMIP – viral macrophage inhibitory protein; vGPCR – viral G-protein coupled receptor; neural cells adhesion molecule family transmembrane protein – N-CAM) [35].

3.1. Epstein Barr virus – EBV

The primary infection by EBV takes place at the oropharingeal mucosa, where the virus infects intra-epithelial B lymphocytes (memory and naïve cells), or lymphocytes adjacent to the epithelial stratum of the mucosa (mainly naïve cells). The infected naïve B cells are then activated, even in the absence of external antigenic stimulus. As a result, the B cell differentiation is blocked and proliferation is stimulated. Some EBV-infected cells are eliminated by cytotoxic T lymphocytes, while others evade the immune response.

EBV-infected-B lymphocytes migrate to germinal center and differentiate to memory cells. During the migration the peripheral blood, the expression of EBV proteins in the infected cells is suspended, so that they mimic non-infected-B lymphocytes. Throughout the division of the infected-cell, DNA replication is carried out by the expression of EBNA-1 EBV protein, which is not properly recognized by the immune system. The viral lytic reactivation occurs when infected-B lymphocytes receive stimulus to differentiate into plasma cells, and the signaling cascade initiated by the B-cell receptor (BCR) results in the expression of the EBV immediately early (IE) genes BZLF1 and BRLF1. Their products activate early genes, and the late lytic genes subsequently. Infected plasma-cells migrate to the oropharingeal mucosa to release infectious EBV particles, which might infect other B lymphocytes or spread via saliva [36].

Based on the expression of different set of viral genes during the latent cycle of EBV, three main distinct latency programs have been described, namely latency I, II and III. Just after the viral entry, nine latent viral proteins are expressed: three Latent Membrane Proteins (LMP-1, LMP-

2a, LMP-2b), six EBV-Nuclear Antigens (EBNA-1, EBNA-2, EBNA-3a/EBNA-3, EBNA-3b/EBNA-4, EBNA-3c/EBNA-6 and EBNA-LP (*leader protein*/EBNA-5), as well as two EBV-encoded small non-polyadenylated RNAs (EBERs/EBER-1 and EBER-2). This expression profile characterizes the latency type III, also known as growth program, as it results in stimulus for proliferation for newly-infected cells. Following migration of the infected-cells to the lymphoid germinal centers, only EBV EBERs, EBNA-1, LMP-1 and LMP-2A are expressed, which characterizes the latency type II. In the germinal center, EBV-infected naïve B lymphocytes differentiated into B memory cells, which migrate to the blood. In this stage there are the expressions of EBNA-1 and EBERs only, the latency type I, also known as the default program [37]. In EBV-associated malignancies, most of the neoplastic infected cells show one of these EBV latency programs, as indicated in Table 2.

3.2. Kaposi's sarcoma herpesvirus – KSHV

KSHV is the most recently-discovered human gammaherpesvirus, described in 1994 [38]. Besides being the causal agent of all forms of KS and PEL [4,5], in HIV-infected patients it is also associated with the development of the Multicentric Castleman Disease (MCD), a rare non-neoplastic lymphoproliferative disorder [39].

The main latent KSHV proteins are the latency-associated nuclear antigen (LANA), encoded by ORF73, the viral homolog for the cellular FAS-associated death domain-like interleukin-1β converting enzyme (FLICE)-like inhibitory protein (vFLIP), encoded by ORF71, and the viral homolog for a cellular D cyclin (vCyc), encoded by ORF72. These three genes are transcribed from the same promoter as latent transcript 1 (5.4 kb), which encodes LANA, vCyc and vFLIP, and latent transcript 2 (1.7 kb), which encodes vCyc and vFLIP [40–42].

The main function of LANA is the maintenance of the KSHV episome (which resembles the function of EBV EBNA-1), which favors viral persistence [43,44]. LANA interacts with the tumor suppressor protein p53 and inhibits its transcriptional activity. As a consequence, genes associated with DNA repair and apoptosis are downregulated [45]. LANA, therefore, favors the survival of KSHV-infected cell, contributing for viral dissemination. LANA can also interfere with the Wnt signaling pathway, as it interacts with glycogen synthase kinase 3-β (GSK3-β) and alters its intracellular distribution, promoting nuclear accumulation of β-catenin, which induces expression of genes as different genes, including *MYC*, *JUN* and *CCDN1* [46,47]. LANA is also able to transactivate the promoter of the human telomerase reverse transcriptase (hTERT), via Sp1 interaction [48,49], favoring cell immortalization. Furthermore, it inhibits its own synthesis, degradation and processing for antigen presentation, which contributes for immune evasion of the KSHV-infected cells [50,51]. These activities make LANA one of the major KSHV oncoproteins.

The first activity attributed to KSHV vFLIP was the negative regulation of apoptosis deflagrated by the tumor necrosis factor receptor (TNFr), as well as inhibition of caspases [52]. However, the main effects of vFLIP expression actually relies on constitutive NF-κB activation, through its interaction with the cellular IκB-kinase [53]. Activation of NF-κB by vFLIP promotes the transcription of NF-κB-dependent anti-apoptotic cellular genes (as the endogenous FLIP and inhibitory apoptosis proteins IAP-1 and IAP-2) [54], and blocks the apoptosis induced by the absence of growth factors [55].

As the endogenous cyclins, vCyc acts in the cell cycle. However, vCyc has preferential interaction with Cdk-6, and the vCyc-Cdk-6 complex is less susceptible to the CDK complex inhibitors $p16^{Ink4A}$ and $p27^{Cip/Kip}$. The vCyc expression stimulates the cell cycle G1 to S progression, inducing DNA synthesis and deregulating the mitosis [56]. Those activities support the proliferation of KSHV-infected cells and the viral propagation as well.

Even in the HAART era, KS still is one of the most common AIDS-related malignancies [57], and the most reported cancer in Equatorial Africa [58]. It is well established that KSHV is necessary, but not sufficient for development of KS [59]. In general, PEL is even less frequent than KS; likewise, however, it is observed more often in immunocompromised individuals, namely under HIV-1 infection [3,60]. Thus, it is plausible to assume that HIV-1 has an important role in the pathogenesis of KSHV-associated cancers.

Table 2
EBV latency programs in neoplastic and non-neoplastic settings (based in Thorley-Lawson and Gross [36]).

Latency	Differently expressed EBV products*	Infected normal B cells	EBV-associated malignancies and lymphoproliferative conditions
Type I (EBNA-1-only)	EBNA-1	Dividing memory cells	BL
Type II (default program)	EBNA-1, LMP-1 and LMP-2a	Germinal center cells	cHL, NHL, NC
Type III (growth program)	EBNA-1, 2, 3a, 3b, 3c, LP, LMP-1, LMP-2a and LMP-2b	Naïve cells	IL, PTLD

* EBERs and BARFs are expressed in all EBV latency programs. BL: Burkitt lymphomas; cHL, classic Hodgkin lymphomas, NHL: non-Hodgkin lymphoma, NC: nasopharyngeal carcinoma, IL: immunoblastic lymphoma; PTLD: post-transplant lymphoproliferative disorder.

4. Viral cooperation implicating HIV, EBV and KSHV

It is noteworthy that EBV-associated lymphomas arise more frequently in the HIV-infected population; as previously mentioned the same is true for KSHV malignancies. Thus, it is plausible to assume that HIV infection and immunosuppression play an important role in the pathogenesis of both EBV and KSHV-associated cancers. Indeed, immunosuppression is a fertile soil for emergence of virally-transformed cells, as they are not properly recognized and eliminated by the host's immune system.

The HIV-driven impairment of the immune system likely contributes for the escape of herpesvirus-infected cells from immune control, allowing their proliferation,

and eventually the emergence of virally-transformed clones [61,62]. For instance, a striking decline in telomere length in EBV-specific CD_8^+ T cells was observed in HIV-positive individuals, compared to HIV-negative subjects. This could lead to an uncontrolled chronic EBV-infection due to a decreased proliferative potential of EBV-specific T CD_8^+ lymphocytes [63], which favors the subversion of the immune surveillance. On the other hand, it is worth to note that KS lesions usually arises in HIV-infected individuals with low T CD_4^+ cells counts [64]. As will be discussed in detail, an increasing body of evidence indicates that the higher incidence of KS in HIV-positive patients, as well as the more aggressive course of AIDS-KS compared to the other forms of the disease, may be related to putative mechanisms of viral cooperation between HIV and KSHV.

One important issue to be considered whenever evaluating plausible mechanisms for viral cooperation in carcinogenesis is the viral cell tropism, since the infected cells are supposed to be the main targets for malignant transformation.

B lymphocytes that express the CR2 (CD_{21}) surface receptor for the C3d complement fragment are the main target cells for EBV infection [65]. EBV DNA has also been detected in the broad CD_{19}^+ B lymphocytes group, as well as CD_4^+ and CD_8^+ T lymphocytes in children and adolescents infected with HIV-1 [66]. Interestingly, it was reported that for $CR2^+$ EBV-transformed B lymphocytes, which usually co-express CD_4, the complex CR2-CD_4 increases the cell susceptibility to HIV-1 entry [67].

Though KSHV has a broad spectrum of cellular tropism, KSHV and HIV also have different target cells for infection. KSHV infects mainly B lymphocytes, keratinocytes, epithelial and endothelial cells [68], whilst HIV infects mainly T CD_4^+ lymphocytes. On the other hand, both may infect dendritic and mononuclear cells [69,70]. It should be noted that the co-localization of KSHV and HIV does not seem to be critical for interaction between these viruses. For instance, in a study published by Aoki and colleagues in 2004, the authors reported that the KSHV infectivity of 293 cells was enhanced when they were incubated with a HIV-1 tat-BR peptide. As the tat-BR peptides were used in concentrations higher than that usually found for the retroviral tat in the serum of HIV-1 patients, it was suggested that lymphoid tissues, where intense HIV replication take place, could be a privileged scenario for KSHV infection of its target cells [71].

Although KSHV and HIV reservoirs of co-infected cells remains to be confirmed *in vivo*, HIV-1 replication in PEL BC-3 cells (KSHV-positive, EBV-negative) *in vitro* was described, and it resulted in KSHV reactivation [72]. On the other side, an increase in HIV replication was observed in HIV-1-infected T CD_4^+ cells co-cultivated with KSHV-infected B cells [73]. Interestingly, the same was observed for HIV-infected monocytes co-cultivated with KSHV-infected endothelial cells [74]. Based on these results, it can be assumed that not only the HIV-1 infection have an important effect for KSHV spread within the host organism, KSHV also contribute for the HIV-1 burden, enhancing AIDS progression.

Possible mechanisms for EBV, KSHV and HIV-1 interaction have the activation of HIV-1 LTR as a converging point, which can be deflagrated by different herpesviral proteins. For instance, the EBV EBNA-2 protein activates the HIV-1 LTR in B cells and HeLa epithelial cells, possibly mediated by the NF-κB signaling [75]. In cell lines transfected with an EBV EBNA-2 expression vector, the protein is also able to enhance the transactivation of HIV-1 LTR via tat. Noteworthy, transactivation of HIV LTR by tat is increased when CD_4^+ cells are infected with EBV type 1, indicating that EBV improves HIV-1 replication in T lymphocytes [76]. It was reported that HIV-1 tat protein has also important effects in EBV-immortalized B lymphocytes, as it is able to change the cell susceptibility to apoptosis and favors cell cycle progression, increasing their proliferative capacity [77].

Other EBV products, as the viral DNA polymerase [78] and LMP-1 [79], also transactivate the HIV-1 LTR, as well as the immediate-early (IE) gene product *Bam*HI MLF1 [80]. The later, however, does not share the tat-responsive elements in the HIV-1 promoter [81]. Further EBV IE gene products capable of inducing the HIV-1 LTR are the BRLF-1, which is either dependent or independent of the HIV-1 enhancer elements [82], and BZLF1, which cooperates with tat in Hela cells [83].

Conversely, KSHV LANA protein activates the HIV-1 LTR in BJAB cells at levels similar or higher than the HIV tat protein. Noteworthy, LANA physically interacts with HIV-1 tat protein through its carboxy-terminal region, and it also synergizes with tat to increase the transcriptional activity of HIV-1 in BJAB, U937 human monocytic cells, and HEK-293T human embryonic kidney cells [84]. Interesting, in Cos7 cells KSHV LANA inhibited the HIV-1 LTR, probably as a result of a negative effect on the NF-kB-dependent transcription. Alternatively, in BJAB cells LANA induced Staf-50 transcription factor, which is an inhibitor of the HIV-1 LTR activity [85]. In addition, the early KSHV KIE-2 protein (viral ORF45) activates HIV-1 LTR when co-expressed with the retroviral tat protein. Interestingly, both HIV-1 tat and vpr proteins activate KSHV KIE2 [86], which may create another amplification loop for LTR activation.

Both EBV and KSHV disturb the NF-κB pathway in the infected cells [87], and this may have a critical effect in the HIV-1 biology. In 293T and Cos7 cells, the HIV-1 LTR may be activated by KSHV vFLIP via the NF-κB-classical pathway, and this interaction is influenced by the number of NF-κB binding sites in the retroviral LTR, which differs according to HIV-1 genotypic strain. Moreover, vFLIP cooperates with HIV-1 tat to synergically activate the retroviral LTR, which result in an amplification loop that enhances tat activity. This could result in an increase in HIV replication, mainly in early stages of HIV-infection or in cells with downregulated tat [88].

As it is becoming evident, the HIV tat protein plays a critical role in many of the putative mechanisms of viral cooperation with EBV or KSHV in human carcinogenesis. Remarkably, the phenotype of the fusiform neoplastic cells in KS is partially attributed to HIV-1 tat activity: this retroviral protein can induce KS-like lesions in nude mice via secretion of interferon-γ (IFN-γ), which has pro-angiogenic properties and it is produced by inflammatory cells present

in KS lesions, notably T lymphocytes CD_8^+ and monocytes/macrophages [89]. The HIV-1 tat induces angiogenesis through the activation of the Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2) in endothelial cells [90]; furthermore, it stimulates the development of KS-like lesions [91,92]. Interestingly, the two-exon-encoded HIV-1 tat – but not the one-exon-encoded version of the protein – promotes growth of the KS cell line SLK in transgenic mice [93].

A relevant link between HIV-1 tat and KS pathogenesis involves the activity of cell surface adhesion molecules. AIDS-KS and normal vascular cells exposed to inflammatory cytokines have increased adhesion due to the expression of the HIV-1 tat. This adhesion is attributable to tat amino acid sequence RGD, which interacts with integrin receptors $\alpha_5\beta_1$ and $\alpha_v\beta_3$. Integrins mediate the growth-promoting effect of HIV-1 tat protein on vascular cells [94]. Moreover, HIV-1 tat mimics matrix proteins, promoting adhesion, migration, and cellular invasion, and also mobilizes the basic fibroblast growth factor (bFGF), which has important angiogenic properties and may enhance KS progression in HIV-infected patients [95].

Another possible mechanism to be considered for viral cooperation involving HIV-1, EBV and KSHV, is dependent on the crosstalk among the biological cycles of these viruses. In this setting, much more is known about the interactions between HIV-1 and KSHV, compared to HIV-1 and EBV.

A decrease in the number of T CD_4^+ lymphocytes early in HIV infection was reported to have an important impact in the control of EBV latency and viral reactivation [96]. Overall, EBV reactivation is inversely related to the T CD_8^+ activity against EBV, so that a progressive impairment in intensity and extensiveness of EBV-directed immune response is observed throughout the natural history of HIV-1 infection [97]. Interestingly, it was previously reported that the retroviral infection activates EBV, as well as upregulates the expression of the c-myc transcription factor in primary human B cells infected with HIV-1, resulting in increased proliferation of EBV-immortalized cells [98]. These observations indicate that the crosstalk between HIV-1 and EBV life cycles not only is relevant, it also urges further investigation, as the available information on this matter in the literature is currently sparse.

On the other side, the mechanisms for the crosstalk between the HIV-1 and KSHV life cycles may be approached considering the main players in viral activation: the HIV LTR and KSHV Rta protein. In BCBL-1 and HL3T1 cells, the interaction between the KSHV Rta (ORF50) and HIV-1 tat protein synergistically transactivates the HIV-1 LTR, probably by a post-transcriptional mechanism. Though KSHV ORF57 also increases the transactivation of the HIV-1 LTR, it does not interact directly with tat, and this effect is possibly due to induction of KSHV Rta. Interesting, transactivation of HIV-1 LTR is partly inhibited when both KSHV Rta and the ORF57 protein were expressed [99]. Additionally, in cell lines permissive to HIV infection (as Jurkat and BC-3), KSHV Rta increases the HIV-1 replication, whilst in HIV non-permissive cells (as A172 glial cells) the expression of KSHV Rta causes vulnerability and transitory permissiveness to HIV infection [100].

It was reported that the HIV-1 activates the KSHV Rt apromoter, causing KSHV lytic replication; this effect relies on proteins other than the retroviral tat [101]. Rather than direct activating KSHV ORF50, HIV-1 tat induce KSHV lytic cycle in BCBL-1 cells through IL-6 expression and activation of the JAK2/STAT3 signaling pathway. In this model, tat stimulates the GATA3 protein, which induces IL-4 expression and activation of STAT6, which in turn influences tat-induced KSHV replication [102]. KSHV replication can also be induced by other cytokines, as oncostatin M (OSM) and the hepatocyte growth factor/scatter factor (HGF/SF), which are produced by, or in response to HIV-infected cells [73].

The anti-retroviral therapy (ART) can prevent the KSHV lytic reactivation in HIV-infected BC-3 cells, and it reduces the transmission of KSHV virions to non-infected cells [103]. Actually, the decrease in KS incidence promoted by ART may indeed be explained in part by the fact that HIV-1 tat increases the KSHV infectivity. As ART decreases HIV-1 burden in the host, there is also a decrease in the production of the retroviral tat, which may explain the detrimental effect of ART in KSHV biology. It should be noted, however, that the levels of HIV-1 tat protein required to increase KSHV infectivity were reported to be 10–15-fold higher than the levels detected in the serum of HIV-infected people [71]. Therefore, the paracrine activity of retroviral tat in KSHV-infected cells may be biologically relevant mainly in sites of more intense HIV-1 replication.

Considering the available body of data, there is substantial evidence that HIV-1 tat really plays a pivotal role enhancing the KSHV oncogenicity in individuals infected by both viruses. HIV-1 tat may even contribute in the KS pathogenesis targeting multiple cellular pathways through KSHV proteins. For instance, it was reported that the retroviral tat increase the KSHV vGPCR signaling, which resulted in accelerated tumorigenesis *in vivo*; of note, there is no requirement of co-expression of HIV-1 tat and KSHV vGPCR in the same cells for this effect [104]. In HUT 78-lymphoid cells, primary endothelial cells, and a KSHV-negative KS-derived endothelial cell line, the HIV-1 tat protein also cooperates with KSHV vGPCR to active the nuclear factors of activated T cells (NF-AT), NF-AT1 and NF-AT-2, and the NF-κB pathway [105]. Importantly, KSHV vGPCR transcripts are detected in AIDS-KS, but not in classic KS samples [106]. Tat also promotes proliferation of the NIH3T3 cells and accelerates tumorigenesis caused by KSHV kaposin A in nude mice, through enhancement of kaposin A-induced signaling involving MEK/ERK, STAT3 and PI3K/Akt [107].

Curiously, KSHV proteins homologs to cellular macrophage inflammatory protein (MIP) may interfere in co-receptors used by HIV-1 for infection of its target cells. The KSHV vMIP-I (ORFK6) attach to CCR5, inhibiting HIV entry and replication of HIV-1 CCR5-variants [108]. KSHV vMIP-II (ORFK4) inhibits the HIV-1 infection of T CD_4^+ lymphocytes [109]. KSHV vMIP-III (ORFK4.1), on the other hand, has an agonist property in CCR4 receptors, being a chemotatractant for peripheral blood T lymphocytes expressing T_{H2} cytokines [110], which manipulates the balance between humoral and cytotoxic responses towards the former. As a result, the immune response became non-

effective to eliminate KSHV-infected cells. Thus, KSHV vMIPs seems to have an important role in KS pathogenesis, and it is plausible to assume that the interference with the availability of HIV-1 co-receptors might contribute to the distinct biological features of classical and AIDS-KS.

5. Mechanisms of viral cooperation in human carcinogenesis: the PEL model

A unique scenario to evaluate the possible interplay between EBV and KSHV in carcinogenesis in the HIV setting is PEL and PEL-based cell culture models. In dually infected PEL cells, KSHV Rta and EBV Zta co-localize and interact physically. The leucine heptapeptide repeat in KSHV Rta and the leucine repeat region in EBV Zta are required for this physical interaction. KSHV Rta is able to inhibit chemically-induced EBV lytic gene expression, and EBV Zta inhibits chemically-induced KSHV lytic expression likewise. EBV Zta and KSHV Rta also interact physically, and it activates the EBV lytic gene expression, although this process could be inhibited by KSHV Rta. As a matter of fact, the initiation of the KSHV lytic cycle do correlates with a decrease in the EBV lytic gene expression [111].

Latently EBV-infected cells that became infected with KSHV show EBV lytic replication; likewise, latently KSHV-infected cells that became infected with EBV reactivate KSHV lytic replication. EBV/KSHV dually-infected cells express EBV LMP-1, which negatively controls the KSHV lytic replication, establishing a regulatory loop with KSHV Rta. LMP-1 is expressed when EBV latently-infected cells became infected with KSHV – as well as in KSHV latently-infected cells infected with EBV – culminating in latency for both gammaherpesviruses in the same cells [112]. Worth to note, KSHV Rta binds to the EBV promoters *in vitro*: in EBV/KSHV dually infected B-cells, the KSHV Rta transactivates the EBV LMP-1 promoter and the C promoter (Cp) through the cellular RBP-Jk transcription factor, culminating in EBV latency type III in a latency I background. LMP-1 protein produced in latency III is responsible for the negative-feedback loop that resulted in the expansion of PEL cells with no need of KSHV reactivation or lysis of the infected-cells, and KSHV Rta contributes indirectly in this effect [113].

It should be noted that viral latency is characterized by the expression of few low-immunogenic viral proteins, so that the immune response against the virus will be diminished. The maintenance of viral latency, therefore, favors the immune escape and confers an increased risk for the development of gammaherpesvirus-associated diseases. On the other side, crucial EBV and KSHV oncoproteins are latency-expressed products: KSHV LANA, for instance, is a multifunctional protein that inhibits the transcriptional activity of the p53 tumor suppressor protein, while EBV LMP-1 constitutively activates the NF-κB signaling pathway in EBV-infected B cells [114]. As it is well known, both the impairment of p53 function and increased NF-κB activation culminate in increased cell proliferation and survival in affected cells. Furthermore, in co-infected PEL cells, the KSHV LANA N-terminal 340-aa tethers to a mSin3

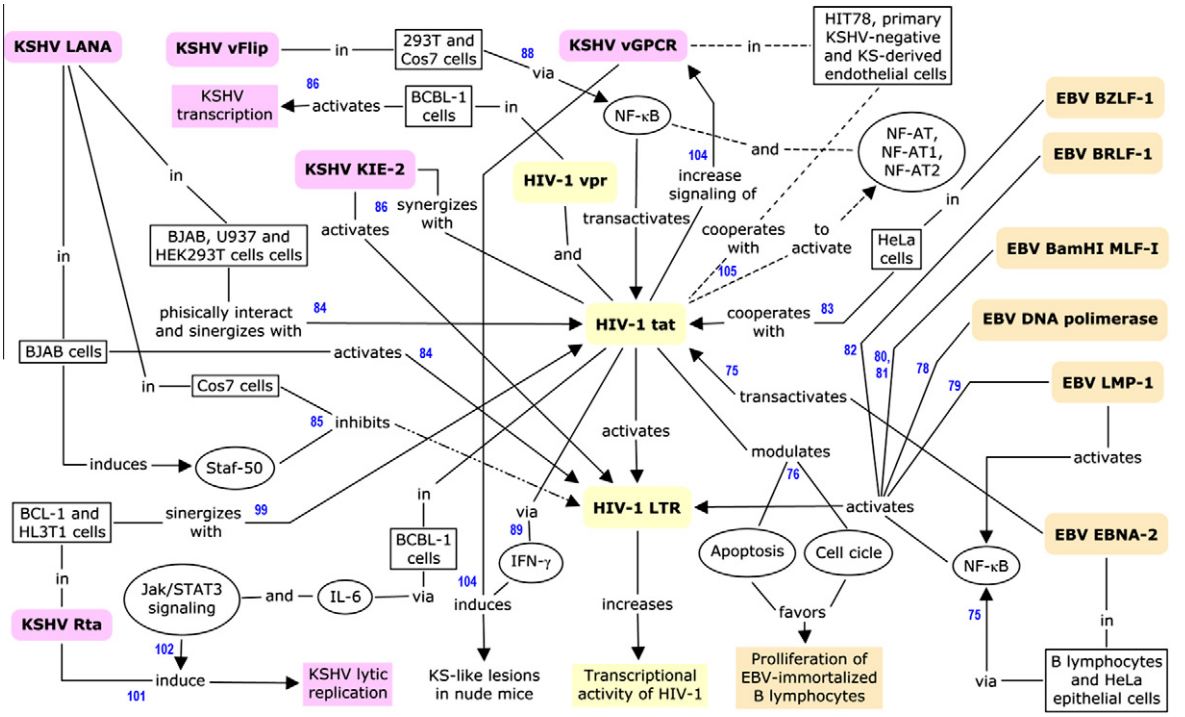

Fig. 2. Concept map produced with the CMapTools Software (Institute for Human and Machine Cognition, Ocala, FL, USA) summarizing the data evaluated in the present review regarding the putative mechanisms for HIV-1, EBV and KSHV cooperation in cell transformation and cancer development in humans. The references for the studies indicating the experimental evidence for the indicated assumption are provided. See text for details.

co-repressor complex to repress the EBV Cp and Qp promoters (which drives the expression of most EBNA proteins and EBNA1, respectively), while KSHV LANA stimulates its own expression [115].

Therefore, it is plausible to consider that the maintenance of viral latency due to EBV and KSHV crosstalk are a key event in PEL pathogenesis.

6. Concluding remarks

The concept map [116] depicted in Fig. 2 summarizes the current knowledge on putative mechanisms for EBV, KSHV and HIV-1 cooperation in human carcinogenesis consolidated in the present review. As can be noted, critical gears in these mechanisms are the HIV-1 LTR activation, HIV-1 tat expression and the regulation of EBV and KSHV biological cycles, with reflect in the expression of major gammaherpesviral proteins with oncogenic potential.

Although disease models in which well-known viral cooperation are sporadic (PEL, for instance), the available evidence points out that possibly we are underestimating the viral cooperation as an important event in the pathogenesis of virally-induced cancers. The same can be also said about infection-associated cancers in general, as we may expect, at least, that more than one infectious agent may play a role an relevant element contributing for the altered microenvironment that give rise to malignant cells. This is a very exciting field for investigation, and it can be expected that in the next years new data will provide us a better understanding of the complex network in which infectious agents participates in carcinogenesis, disclosing new and important information on cancer biology itself.

Conflict of interest

The authors have no conflicts of interest to disclosure.

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