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BIOLOGY OF KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS

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1. ABSTRACT

Kaposi's sarcoma-associated herpesvirus (KSHV) or human herpesvirus-8 (HHV-8) is a newly identified herpesvirus. KSHV is an important pathogen capable of causing disease that affects all age groups worldwide. KSHV is etiologically associated with all forms of Kaposi's sarcoma (KS), body cavity lymphomas, and multicentric Castleman disease (MCD). The use of highly active antiretroviral therapy (HAART) since 1996 has markedly reduced the prevalence of KS in western countries, but because 99% of the 40 million patients with AIDS in the world cannot afford HAART, KSHV pathogenesis is still a very common problem. In this chapter, we delineate some of the latest findings about KSHV infection and pathogenesis.

2. INTRODUCTION

Kaposi's sarcoma-associated herpesvirus (KSHV), which is also known as human herpesvirus 8 (HHV-8) belongs to the *Herpesviridae* family (1). Currently there are eight known human herpesviruses, of which KSHV is the most recently identified herpesvirus (2, 3). The seven other human herpesviruses of the *Herpesviridae* family are; herpes simplex virus type 1 (HSV-1; Human herpesvirus 1), herpes simplex virus type 2 (HSV-2; human herpesvirus 2), varicella-zoster virus (VZV; human herpesvirus 3), Epstein-Barr virus (EBV; human herpesvirus 4), human cytomegalovirus (human herpesvirus 5), human herpesvirus 6, and human herpesvirus 7 (4).

Table 1. Gamut of KSHV associated disease conditions

Disease condition	KSHV association	Is KSHV an etiology?
KS, PEL, MCD	KSHV has been conclusively demonstrated to be etiologically associated with the disease conditions (2, 3, 13).	Yes.
Prostate tumors	1) KSHV DNA sequences have been detected in specimens from the prostate tissue by various research groups over the years (14). 2) Recent studies also demonstrated an elevated seroprevalence of KSHV among men with prostate cancer (15-18). 3) No staining for LNA-1 was observed in samples from prostate cancer supporting the absence of any etiological link between this disease and KSHV (19).	?
Sarcoidosis	1) KSHV DNA sequences have been found in a wide range of sarcoid tissues (20, 21). 2) KSHV sequences were not detected in sarcoid tissues from Greek and French patients (22, 23). 3) There is no evidence for a role of KSHV in sarcoidosis either at the molecular or at the level of serology (24).	?
Salivary gland tumor	1) KSHV DNA sequences was detected in a case of a bilateral parotid mucosa-associated lymphoid tissue (MALT) lymphoma associated with 2 years history of Sjogren's syndrome (SS) (25). 2) A case of KS of an intraparotid lymphnode was reported in a 57 year-old patient (26). 3) KS of the major salivary gland is rare; but cannot be completely ruled out. The authors reported the presence of KSHV in all the 6 salivary gland tumors screened (27). 4) KSHV does not usually infect the salivary gland in HIV-seronegative patients and does not seem to play a pathogenic role in vascular and epithelial salivary gland neoplasm (28, 29).	?

"?" indicates that the role for KSHV as an etiology has not been conclusively established for the particular disease condition.

The *Herpesviridae* family contains many large DNA viruses whose natural hosts are mammals, vertebrates, and one invertebrate (5, 6). Herpesviruses are predominantly responsible for chronic infections that recur in individuals with compromised immune systems (7). The numerous viruses contained in the *Herpesviridae* family are divided up into the three subfamilies, *Alpha*-, *Beta*-, and *Gammaherpesvirinae* (6). The *Gammaherpesvirinae* subfamily of *Herpesviridae* is divided further into two genera: *lymphocryptovirus* (γ1 group) and *rhadinovirus* (γ2 group) (8). KSHV is the only known γ2 herpesvirus that infect humans (9). The oncogenic EBV, which is a γ1 virus, is the closest related human herpesvirus to KSHV (8, 9).

3. KSHV PATHOGENESIS

KSHV was first discovered in a Kaposi's sarcoma (KS) lesion in 1994 (2). The virus primarily infects and establishes latency in two cell types; endothelial cells and B-lymphocytes (10, 11). KSHV can also infect other cell types, but with limited effectiveness. Human herpesvirus 8 has been etiologically linked to Kaposi's sarcoma (KS) and because of this link is now referred to as KSHV (12). KSHV is also etiologically associated with primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD) (13, 30, 31). There has also been inconsistent data presented concerning a role for KSHV in the progression of other malignancies such as prostate cancer, sarcoidosis, and salivary gland tumor (Table 1).

KS is a highly vascular tumor that originates from endothelial cells. KS is described as proliferation of multiple independent lesions that have a vascular and neoplastic origin that could turn into nodular tumors that are localized in the skin and visceral organs (20). The cells in KS lesions are spindle-shaped cells which are infiltrated by inflammatory cells (32, 33). A majority of the spindle-shaped cells are found in the nodular stage of KS lesion (34). *In vivo,* productive (lytic) infection is restricted to only a small fraction of cells at any given point of KS progression. Several lines of evidence points to the fact that the lytic infection is always low and confined to a very small fraction of cells including monocytes and T cells infiltrating KS lesions (35-37). Several variations of the KS have been identified that vary in aggressiveness of infection and morbidity (38). The four forms of KS are classical KS, endemic or African KS, AIDS-KS, and iatrogenic or transplantation associated KS.

Classical KS was described by Moritz Kaposi in 1872 and was originally observed in elderly men of European and Mediterranean descent. It is a mild form of the disease condition. Endemic KS is a lymphatic disease of the legs that is presented as lymphedema which is etiologically associated with barefoot exposure to the volcanic soils in certain regions of Africa (39). Most endemic KS occurs in a band that crosses equatorial Africa. Because of AIDS, the already prevalent endemic KS in Africa is now at an epidemic level and it is now impossible to independently study the disease (40). AIDS KS is found primarily in homosexual and bisexual men who have AIDS (41). AIDS KS is extremely aggressive and shows a higher frequency of mucosal progression than the other forms of KS (42). The lesions are presented multifocally and are commonly found on the upper body, neck and head (43). The lesions evolve rapidly and spread viscerally which is responsible for the high mortality due to the organs becoming dysfunctional (40). Iatrogenic KS is common in persons after transplantation, especially kidney transplantation that accounts for up to 80% of all

malignancies in kidney transplant recipients (44). This is due to the immunosuppressive drugs taken by the patients to prevent rejection of their organ transplant. Recently, a new form of KS (micronodular KS) has been proposed as a variation of KS that mimics capillary hemangioma in an HIV-seronegative, middle-aged Caucasian woman (45).

Primary effusion lymphoma is a rare form of B cell Lymphoma that is observed mostly in individuals who are co infected with HIV, EBV, and KSHV, but there have been cases of individuals who were HIV- and EBV-seronegative with PEL (46). PEL primarily manifests itself in body cavities; lymphadenopathy and solid tumors are rarely observed, but cases of soft-tissue masses have been reported (20). This plasma cell lymphoma has no cell lineage markers, but is recognizable by the high number of viral DNA copies per cell and the monoclonal immunoglobulin rearrangements; both features are unique to PEL (47, 48).

Multicentric Castleman disease is also a lymphoproliferative disorder that has many similarities to PEL with some key differences. MCD is even rarer than PEL and is distinguished by proliferation of polyclonal B cells (49). Unlike PEL, MCD is not associated with EBV and only a small percent of all cases are KSHV positive; and those that are KSHV positive are called MCD plasmablasts because of the presence of large KSHV positive plasmablasts (10). MCD also differs from PEL by the fact that there are no immunoglobulin rearrangements; MCD doesn't constitutively express high levels of CD30; almost always MCD has high concentrations of cytoplasmic IgM present; and MCD is found in multiple lymphadenopathy (43).

4. KSHV INFECTION AND PATHOGENESIS

4.1. KSHV entry

KSHV infects a variety of target cells *in vitro*, and that includes human B cells, endothelial cells, epithelial cells, fibroblasts, and keratinocytes (50-55). KSHV express a variety of glycoproteins on the envelope layer on the same lines as other herpesviruses. KSHV open reading frames (ORFs) 8, 22, 39, 47, and 53 encode for envelope associated gB, gH, gL, gM, and gN, respectively, that are highly conserved within the herpesvirus family (1, 56). In addition to the above, gene K8.1 ORF encodes for envelope associated gpK8.1A and gpK8.1B that is unique to KSHV (57). KSHV gpK8.1A and gpK8.1B are splice products from two ORFs derived from K8.1 gene (58). Of the both, it is gpK8.1A that is predominantly detected within the infected cells and on the virus envelope (59). Herpesvirus entry process involves complex interactions between the virion envelope associated glycoproteins and the receptors expressed on cell membrane (60). Similar to HSV, KSHV encoded gB, gH, and gL were demonstrated to mediate cell-cell fusion in an *in vitro* luciferase reporter gene activator assay (61). This property of glycoproteins to mediate fusion is very crucial for the entry process. In addition, neutralizing antibodies directed towards gB, gH, and gL significantly inhibited KSHV infection of target cells at a post-attachment stage of entry suggesting a role for these proteins in the entry process (62, 63). On the contrary, studies by Luna and others conclusively demonstrated that the gpK8.1A was not a requirement for the virus entry in 293 cells using a K8.1-null recombinant virus (BAC36DeltaK8.1) (64).

KSHV, like other herpesviruses binds target cells via interactions with heparan sulfate (HS)-like moieties expressed on the target cells (50). This interaction between the virus and the HS on the cell membrane is mediated by envelope glycoproteins gB and gpK8.1A (62, 57, 65). We determined that the initial binding to target cells via HS is purely a charge-based interaction (62). Based on our results, we concluded that the virus infects a variety of target cells *in vitro* because of its ability to bind a ubiquitous molecule such as HS.

KSHV utilizes integrins as one of the entry receptor molecules. As of this day, the integrin molecules identified to have a role in the virus entry are $\alpha 3\beta 1$, $\alpha v\beta 3$, and $\alpha v\beta 5$ (66-68). KSHV interacts with integrins on the cell membrane via the RGD (Arg-Gly-Asp) motif present in the envelope associated gB which facilitates virus entry into cells (66). The RGD motif is the smallest peptide region of proteins that are known to interact with subsets of host cell surface integrins. Interestingly, KSHV gB is the only known animal and human herpesvirus gB that possess the RGD motif to bind integrins. The RGD sequence within the gB of various KSHV strains (a total of 63 strains) from different geographical locations is highly conserved (69). Herpesviruses in general are understood to enter target cells via fusion at the level of cell membrane (70). Studies using purified virus, electron microscopy, confocal microscopy identified KSHV enters human foreskin fibroblasts (HFF) primarily via endocytosis (67). KSHV entry in HFF cells was predominantly via clathrin mediated endocytosis. But it should be remembered that the virus entry is a complicated process that varies according to different cell types and specific signaling. KSHV utilizes an altered entry pathway in 293 cells: KSHV utilizes HS to bind the cells but the entry is independent of RGD binding integrins (71). Another good example for such different mechanisms used by the same virus in different cells is HSV-1: HSV-1 is generally believed to enter target cells via fusion of envelope at the level of cell membrane (72); however, latest studies claim HSV-1 and HSV-2 to enter HeLa and CHO cells via endocytosis (73). Based on the already available literature, we predicted KSHV entry into normal cells to follow endocytosis involving the cytoskeleton machinery (Figure 1) (63, 66). Actin cytoskeleton plays an important role in the entry of several viruses. The microtubules and/or microfilaments are also known to be critical in directing the intracellular movement of viruses (74, 75). In a recently concluded study it was demonstrated that microtubules play a critical role in KSHV entry process in HFF and 293 cells (76). Based on the present studies, we propose a model for KSHV entry into target cells (Figure 1).

4.2. Effect of oncoproteins on KSHV infection of cells

KSHV is typically a tumor causing virus. Kaposi's sarcoma lesions are said to express elevated levels

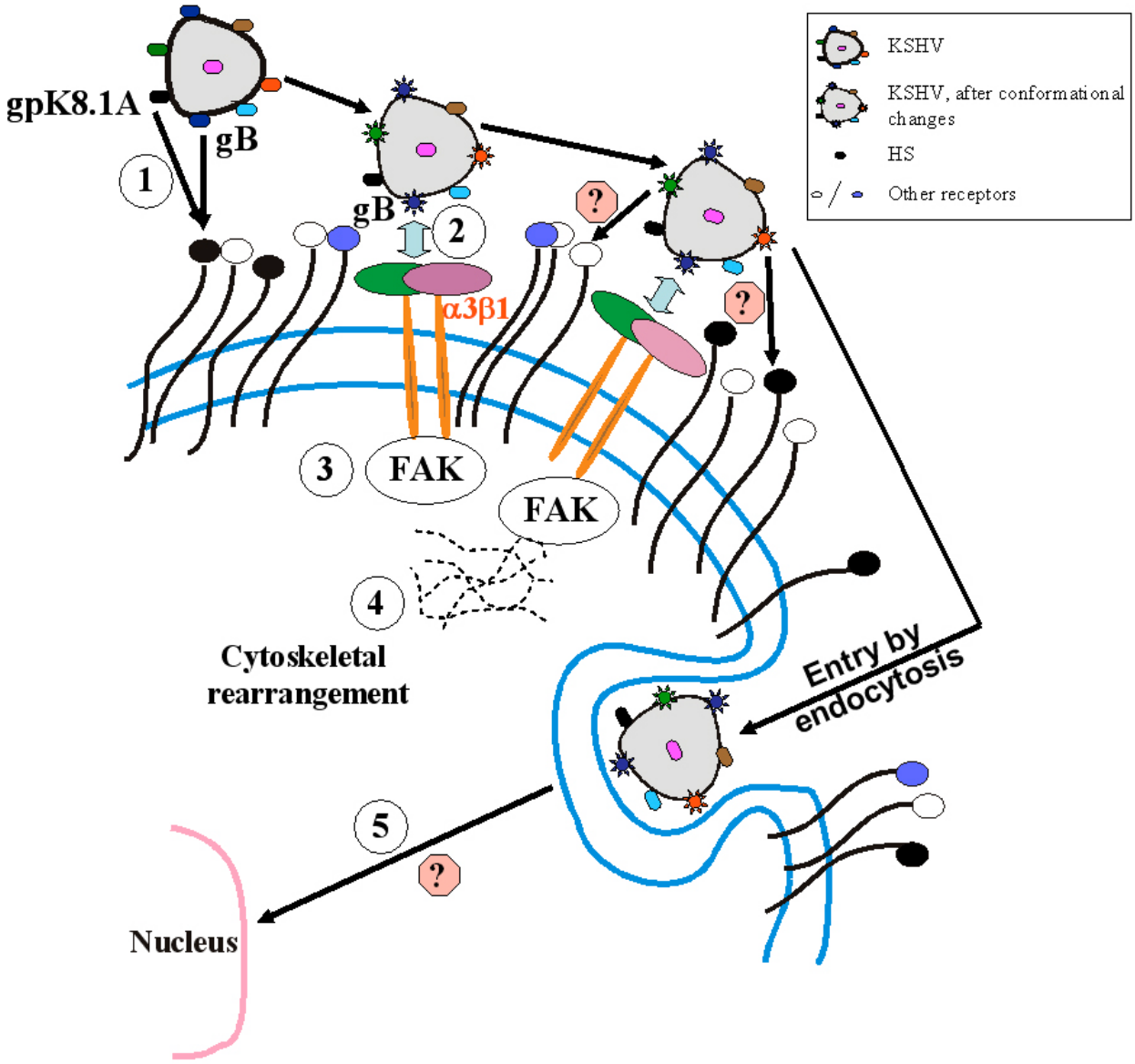

Figure 1. Model to explain KSHV entry process. Virus entry process is a complicated event that involves a well-orchestrated interaction between various molecules expressed on the virus and the target cells. Based on others and our results, we propose a model for the virus entry process. Stage 1: KSHV binding to target cells is the first critical step that can initiate virus entry process. This initial binding process is mediated by the virus interacting with HS-like moieties that are ubiquitously expressed by target cells; Stage 2: Initial binding allows virus to concentrate on the cell surface. It also probably facilitates conformational changes on the virus envelope allowing interactions between envelope associated gB and RGD binding integrins α3β1 (66). KSHV is also known to interact with other entry mediating integrins such as αvβ3, and αvβ5 (67); and Stage 3 and 4: This virus-integrin interaction induces a FAK associated signaling leading to cytoskeletal (actin/microtubules/microfilaments) rearrangement leading to the eventual virus entry. It is still not clear about other complex and yet to be identified signaling events (?) that can also induce cytoskeleton changes crucial for the virus entry via endocytosis (Stage 5). At this point we are far from completely understanding the virus entry process. However, earnest efforts are being made by others and us to decipher such a complex phenomenon.

of Ras (77). Mutation in Ras has been detected in the late nodular KS lesions (78). Recently, we demonstrated an elevated Raf/MEK/ERK signaling in KSHV infected hematopoietic cells (79). However, we did not find any mutation in the exon 11 and 15 of B-Raf isoform. Raf holds a pivotal position in the Ras/Raf/MEK/ERK signaling pathway (80). In addition, constitutive activation of the components (Ras/Raf) of the MAPK pathway of signaling has been associated with a variety of tumors; including AIDS-related KS (81). Hence, we analyzed the

effect of oncoprotein Raf on KSHV infection of cells. Raf expression enhances KSHV infection of target cells (82). Raf signaling also regulates a variety of growth factors (GFs) that includes both vascular endothelial growth factor (VEGF) and heparin binding epidermal growth factor (HB-EGF) in both human foreskin fibroblasts (HFF) and in PEL cells (79, 82). In two separate studies, we demonstrated that the Raf induced VEGF has the potency to augment KSHV infection of cells (83, 84). Overall, Raf signaling had a positive impact on KSHV infection of cells, from the virus point of view. However, understanding the effects of oncoproteins on KSHV infection of target cells is still in its infancy; and efforts to understand such a role of oncoproteins on KSHV infection are underway in my lab.

5. PROTEINS CRUCIAL IN KSHV MEDIATED PATHOGENESIS

Proteins encoded by the virus as well as by the cells play an important role in KSHV mediated pathogenesis.

5.1. Proteins Encoded by the Virus

KSHV carries 11 ORFs that encode homologues to cellular proteins involved in signal transduction, cell cycle regulation, and/or inhibition of apoptosis (20). Four of these genes, K9 (viral interferon regulatory factor; vIRF), ORF-74 (KSHV viral G protein-coupled receptor; GPCR), ORF-K1, and ORF-K12 can transform rodent cells and/or cause tumors in animal models (85-88).

KSHV infection can be either latent or lytic. The aforementioned genes separate the two stages, therefore endorsing the classification of individual gene expression to be important in foretelling their pathogenic responsibilities. In vitro, KSHV infection of cells results in a latent infection. Latency is characterized by the presence of viral genome in the form of episome, with highly restricted viral gene expression and lack of virus production (40). In the past, determining the classification of the viral genes was complicated due to a small group of cells undergoing spontaneous reactivation when they were analyzed. However, a solution was found when KSHV was analyzed at the single-cell level by in-situ hybridization (40). The K12 gene is the most abundant transcript expressed in latent KSHV infection of cells (89). It transforms cultured cells and drives tumorigenesis when these cells are introduced to nude mice (40). In contrast, K1, K9, and ORF-74 are associated with lytic replication. The viral gene, ORF50, switches KSHV from latency to lytic replication (90). The viral K1 gene encodes a unique transmembrane protein capable of transforming T lymphocytes experimentally (91). KSHV ORF K9 encodes the viral protein vIRF which is similar to the interferon regulatory factor protein family, thus, through its similarities, holds antagonistic anti- and pro-oncogenic properties (92). ORF-74 or vGPCR is most homologous to the human receptor for IL-8 (93). Experimental results implicate ORF-74 in inducing angiogenesis via enhancing the expression of angiogenic inducer, VEGF (94).

5.2. Proteins Encoded by the Cell

Activation of the immune system due to flustering and infiltration of KSHV are involved with KS commencement. Furthermore, the success of KSHV infection is contingent upon GFs and inflammatory cytokines (ICs) (3, 95, 96). GFs/ICs are proteins that are normally produced in small amounts within the cell (97). They bind to other cell surface receptors leading to cellular proliferation and differentiation. Other functions of GFs and ICs include: activation of endothelial cells (EC), recruitment and activation of lymphocytes, reactivation of KSHV, and induction of phenotypic and functional properties associated with KSHV-infected spindle shaped cell morphology (43, 88). GFs and ICs are said to control various cellular functions by an autocrine/paracrine initiation of cell signaling cascades that increase the activation of multiple transcription factors (84). A few typical GFs and ICs that play a crucial role in the KSHV mediated pathogenesis include: interferon-gamma (IFN-γ), tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, VEGF, basic fibroblast growth factor (bFGF), and oncostatin-M (OSM). The role of various GFs/ICs in KSHV pathogenesis is discussed in detail in a recently published work (80, 95).

Of all the GFs/ICs mentioned above, VEGF is said to play a crucial role in KSHV pathogenesis (98-101). VEGF is a multifaceted protein that has been implicated to play a paramount role in a growing number of processes including angiogenesis, proliferation, differentiation, migration, cell survival, regulation of leukocyte-mediated inflammation, activation of oncogenes, vascular development, and cell permeability (102). Signal transduction through VEGF receptors induces the expression of a gamut of cytokines and GFs, but importantly, it also induces the expression of VEGF and VEGFR (103). Thus it elicits a positive feedback loop that results in autocrine activation of cells (102). Recently, studies have shown that both VEGF and its related receptors are upregulated in tumor angiogenesis and proliferation (100). Tumor formation is a direct result from angiogenesis, inflammation, and proliferation. VEGF is a factor that has been identified to be involved in all aspects of vascular development: vasculogenesis, angiogenesis, vessel recruitment, and specialized differentiation (104). Interestingly, VEGF associates with bFGF and mediates its effect on the cells (105). In addition, we also determined that VEGF is not a requirement for KSHV infection; however, VEGF plays a major role in augmenting KSHV infection of cells at a post cell-attachment stage of entry (83, 84).

6. TREATMENT

There are several approaches to treat KSHV pathogenesis. The only topical compound that is approved by the FDA for the treatment of skin lesions associated with KS is alitretinoin (0.1%). The gel is applied three to four times a day and has been demonstrated to be effective (106). Cryotherapy and radiation therapy has been successfully used to treat KS lesions (107). Cryotherapy kills the cells in the lesion and promotes growth of healthy cells. Intralesional therapy using vinblastine (a chemotherapy drug) can be injected directly into the lesion which has been successfully used to treat local lesions on the skin

(108). However, chemotherapy is usually preferred when the lesions are spread all over the body.

The first order of treatment utilizes highly active antiretroviral therapy (HAART). This method of treatment is best recognized when used against human immunodeficiency virus (HIV). The effects of HAART have been associated with a decline in the frequency of acquired immunodeficiency syndrome Kaposi's sarcoma (AIDS-KS) (109). Since KSHV is the recognized mediator of KS, it is fair to look towards this virus as one target for treatment. The treatment of the disease is dependent on the stage of the condition. For "limited" disease, local therapy or non-bone marrow suppressive agents can be used; and for "extensive" disease, new chemotherapeutic agents can be used such as liposomal anthracycline (110). Cidofovir, foscarnet and gancyclovir are some of the best known anti-virals that are known to significantly reduce KSHV viremia (111, 112). Finally, interferon-α (INF-α) is the only immunomodulant agent to have shown a therapeutic effect among the several tested to date (113).

7. PERSPECTIVE

For successful treatment of KSHV infection, we must have a greater understanding of the virus and its biology. There are several other novel ideas suggested to be the therapies in the future to cure KSHV mediated pathogenesis based on recently conducted studies. RNA interference can be used in the future as a potential tool against KSHV infection and pathogenesis (114). A greater understanding of the disease condition will help us better in targeting the expression of a specific gene(s) by adopting an efficient delivery technique. In addition, targeting Raf/MEK/ERK and VEGF/VEGFR signaling that regulate different stages of tumorigenesis could well be a design of developing anti-cancer/viral drugs for the future (80). Over all, the use of HAART since 1996 has markedly reduced the prevalence of AIDS in western countries, but because 99% of the 40 million patients with AIDS in the world cannot afford HAART, KS is still a very common problem (32). Hence, the need for the future is a novel design of therapy that is also cost effective.

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