WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 5, 891-906. Review Article ISSN 2277– 7105

KAPOSI SARCOMA –A MOLECULAR OUTLOOK

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Article Received on
07 March 2015,

Revised on 30 March 2015,
Accepted on 20 April 2015

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ABSTRACT

Kaposi's sarcoma–associated herpes virus (KSHV) [or human herpes virus 8 (HHV-8)] is the most successive reason for threat among AIDS patients. KSHV and related herpes viruses have widely pilfered cellular cDNAs from the host genome, giving a unique chance to investigate the scope of viral mechanisms for controlling cell proliferation. A large portion of the viral regulatory homologs encode proteins that straightforwardly repress host adaptive and innate immunity. Other viral proteins focuses retinoblastoma protein and p53 control of tumor suppressor pathways, which additionally assume key effector roles in intracellular immune reactions. The immune evasion strategies utilized by KSHV, by focusing on tumor suppressor pathways actuated amid immune system signaling, may prompt coincidental cell proliferation and tumorigenesis in susceptible hosts.

KEYWORDS: KSHV, HHV-8, antiviral immunity, tumor virus, viral oncogenes.

INTRODUCTION

Kaposi sarcoma (KS) is a profoundly vascularized tumor that fundamentally influences the skin.[1] It can likewise disperse to lymph nodes and viscera amid disease development.[2] Four clinico-epidemiologic types of KS have been portrayed and assigned as classic, endemic, iatrogenic, and pandemic (because of HIV contamination).[3-4] In a few African districts, pandemic KS is the most recurrently diagnosed tumor and in 2014, the number of KS cases globally was assessed to be approx. 85 000, or 1.5% of all diagnosed cancer[5] (*Figure: 1*).

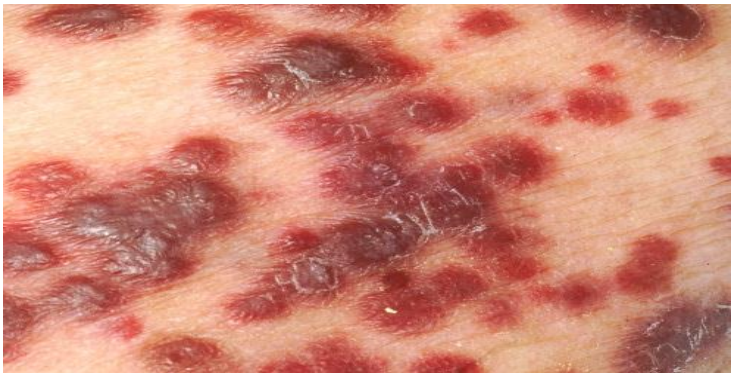

Figure: 1 Clinical Manifestation of Kaposi Sarcoma

Lesions of the four KS forms consist of three major cell types: endothelial cells, spindle cells, and infiltrating inflammatory cells.[6] Spindle cells derived from lymphatic endothelial cells and are the principle cell type exhibited in last stage (i.e., nodular) lesions that form very much defined fascicles.[7-8] HHV-8, is found in spindle cells at all KS stages. Found in a biopsy of a patient with pandemic KS, HHV-8/ KSHV is the only known human 2-herpesvirus.[9] Its genome comprises of a 140-kb region that enclose more than 90 genes and is flanked by various GC-rich terminal repeat (TR) sequences of 803 bp each.[10-12] Despite the fact that a few theories as to the singular roles of specific HHV-8 genes in KS pathogenesis have been proposed, the precise role of every HHV-8 gene in the initiation and progression of KS is still under scrutiny.[13] The expression of HHV-8 inert genes (LANA-1, v-cyclin, v-FLIP) in almost all tumor spindle cells and the little part (around 1%) of these cells that express markers of HHV-8 lytic replication recommend that HHV-8 is in an inert state in KS[14-16] (*Figure:2*). KSHV is a double stranded DNA herpes virus belonging to the gamma herpes virinae subfamily. KSHV has been connected with the development of three neoplastic disease: Kaposi sarcoma (KS), multicentric Castleman disease (MCD) and primary effusion lymphoma (PEL).[17]

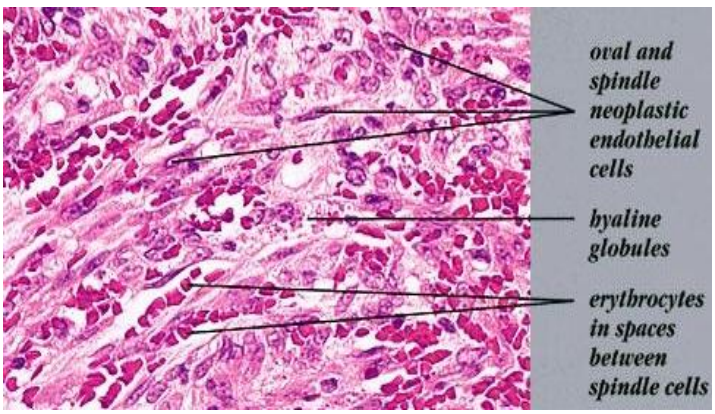

Figure: 2 Micrograph of Kaposi Sarcoma lesion

Histologically, the KSHV-contaminated cells are spindle shaped, inadequately separated, and very proliferative. KS is likewise described by extravasation of erythrocytes, invasion of incendiary cells (macrophages, lymphocytes and plasma cells) and neo- angiogenesis.[18] Clinically, KS is described by dermatological lesions that are red, cocoa, or purple in pigmentation. These lesions can be discovered cutaneously, mucosally, or viscerally. KS can be organized by six overlapping clinico pathologic forms: infiltrative, florid, nodular, patch, plaque, and lymphadenopathic. It is vital to note that more than 95% of KS lesions consist of KSHV viral DNA.[19]

The colossal lion's share of the human cancers are clonal pathologies, signifying that the tumor cells derived from a special substantial cell taking after a process that includes deification or mutation. Consequently, tumor cells show indistinguishable markers, which can be diverse for every cancer. Investigation of these markers permits us to recognize between a real cancerous lesion and one derived from a non-neoplastic extension of cells. Clonality studies are therefore treasured for comprehending tumor pathogenesis and in the diagnostic and follow-up of the pathology.[20-21] Till date, the evaluation of Clonality in KS, utilizing cell clonality markers, has produced conflicting results. Still to be determined is whether multicentric (i.e., spread) lesion begin as metastasis from a primary lesion or on the off chance that they relate to autonomous cell proliferation events. The utilization of a solid clonality marker for KS can permit us to determine these two concerns[22] (*Figure: 3*).

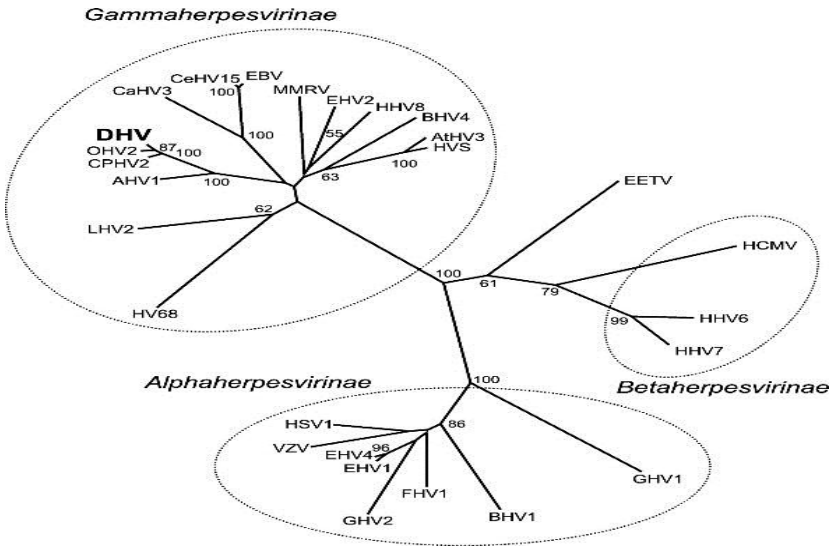

Figure: 3 Phylogenetic Tree of known Human herpes virus

In virally impelled tumors , the exhibition of a specific viral clonal pattern has been influential in linking a given virus to a specific tumor.[23] One outline of the estimation of this

methodology is the work that connect the human onco-retrovirus HTLV- I with adult T-cell leukemia. Since HTLV-I incorporates its provirus arbitrarily into host chromosomal DNA, monoclonal reconciliation of HTLV-I provirus shows the clonal multiplication of HTLV- I–infected cells.[24-25] Consequently, exhibit of clonality of HTLV-I proviral DNA is crucial to finding of adult T-cell leukemia and to support that HTLV-I is the causative marker of such a tumor cell expansion.[26] Besides, on account of herpes viruses, a methodology that utilized the size of the Epstein-Barr virus (EBV)–fused TR area as a molecular marker for clonality exhibited that EBV-related nasopharyngeal carcinomas are monoclonal and demonstrated that EBV infection leads monoclonal expansion of some non-Hodgkin lymphomas including Burkitt lymphoma.[27]

KSHV Genome

The long unique region (LUR), which is around 138 to 140.5 kb long and contains the greater part of the KSHV ORFs, is flanked by terminal repeat (TR) sequences at both ends of the linear viral genome(*figure:4*). Every TR is 801 bp long and is exceedingly GC-rich.[28-29] The quantity of TRs fluctuates among KSHV secludes, extending from 16 to 75, which represents the variation in the genome sizes of KSHV isolates. The KSHV genome shows high level of similarity to retroperitoneal fibromatosis-associated herpes virus (RFHV) and rhesus monkey rhadinovirus (RRV) in the rhadinovirus subfamily of gamma herpes virinae.[30] RFHV has all the earmarks of being more nearly identified with KSHV. Albeit a large number of the KSHV ORFs are rationed in alpha- and beta-herpes viruses, the virus does contain unique ORFs not found in different herpes viruses. These KSHV-particular ORFs are assigned K1 to K15, taking into account their relative position in the KSHV genome. Additionally, KSHV likewise contains a few viral genes that have been pilfered from the host genome and are homologues of cellular genes.[31]

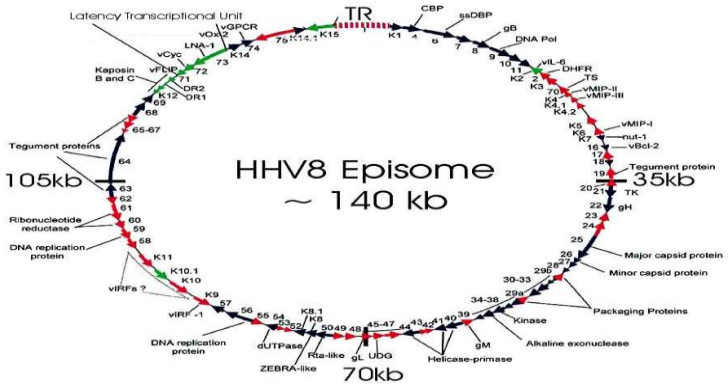

Figure: 4 Genome of HHV-8

Numerous viral genes are included in signal transduction (e.g. K1, K15), cell cycle regulation (e.g. vCyclin, LANA-1), restraint of cell death (e.g. K1, vFLIP, vBcl-2) and immune modulation (e.g. viral chemokine receptors, vIRFs, K3, K5).[32] Furthermore, various KSHV genes are expressed by alternate splicing, by the utilization of transcriptional start sites, or internal ribosome entry sites (IRES).[33]

Recently, an aggregate of 12 microRNAs have been found in the KSHV genome.[34] Ten of these microRNAs were found in the non-coding region between K12/ Kaposin and K13/Orf71/vFLIP, and two were situated inside the K12 ORF.[35] The greater part of the KSHV microRNAs were expressed amid latency with a sub-set of these microRNAs being up regulated amid the lytic cycle. Latest proof has distinguished cellular and viral target of these microRNAs, and their roles in KSHV pathogenesis.[36] Other than microRNAs, KSHV additionally produces a non-coding RNA transcript that is 1077 bp in size, polyadenylated and exclusively nuclear (PAN). PAN RNA is made amid the lytic cycle and has been indicated to hold intron less RNA in the nucleus and square the assembly of an export competent mRNP.[37]

KSHV Gene Expression

KSHV gene expression relies upon a mixed bag of factors including whether the virus is inert or lytic, the type of host cell infected, and the host cell environment[38-39] (*Figure: 5, 6*). At the point when instigated into lytic replication, the virus genome imitates through a moving circle mechanism with individual viral genomes being cut in the terminal repeat region and bundled as linear particles into viral capsids.[40]

A remarkable feature of the genome uncovers itself when the functions and expression pattern of the genes are investigated: Structural genes and highly conserved genes included in lytic replication have a tendency to bunch in islands divided by novel genes, including a large portion of the cDNA homologs of cell regulatory genes. At the point when KSHV enters lytic replication, the cluster of lytic replication genes are induced in an organized cascade.[41-43] Gene cluster have more confounded expression pattern, and numerous genes are expressed at low levels amid latency however are impelled amid lytic replication, an example alluded to as class II translation, recognizing it from constitutive (class I) or lytic (class III) expression.[44]

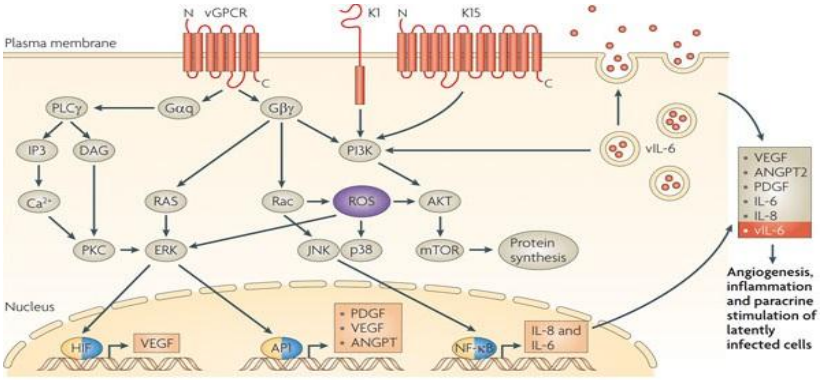

Figure: 5 Lytically infected cell expression in HHV-8

Unscrambling gene expression amid lytic and latent replication has been helpful for classifying KSHV genes, yet it is clear that totally unrelated latent and lytic gene classifications are so shortsighted, it couldn't be possible to portray the biology of KSHV.[45-47] For instance, ORF K10.5 [latency-associated nuclear antigen (LANA2)] is just constitutive in hematopoietic cells however not in KS tumors, and even the constitutive genes encoding vFLIP (FLICE-inhibitory protein), vCYC (cyclin), and LANA1 at the real latency locus are expressed in a G1/S cell cycle–dependent pattern.[48] vIL-6 is impelled amid lytic replication but at the same time is actuated by interferon (IFN) signaling autonomous of replication cycle. Phorbol ester treatment might specifically actuate a few genes, for example, ORF K5 [modulators of immune reaction (MIR2)], further convoluting whether these viral genes are singularly initiated amid lytic replication.[49-51] Two genes, ORF K12 (Kaposin) and ORF K7 (PAN, polyadenylated nuclear RNA), which are expressed and regularly utilized as markers for latent and lytic virus replication, individually, are instigated amid lytic replication in PEL cells. This many-sided gene is not startling on the grounds that KSHV is an extensive infection with the ability to react in complex ways to its cellular surrounding.[52]

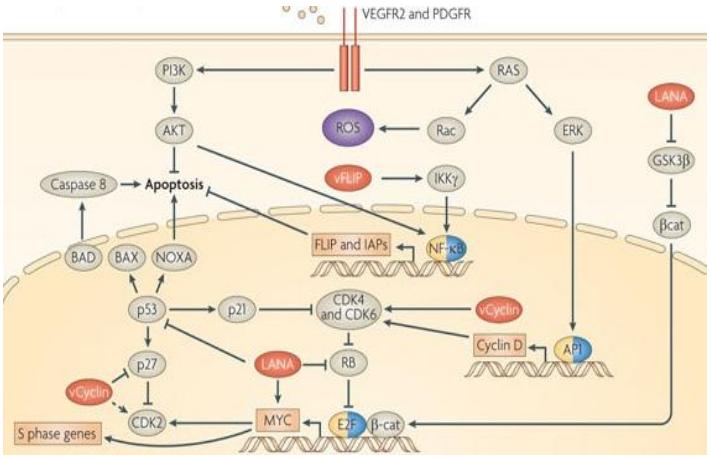

Figure: 6 Latently infected cell expression in HHV-8

Antiviral Therapy

Inhibitors of herpes virus DNA polymerase will be compelling in fighting lytic however not dormant DNA contamination.[53] Foscarnet and ganciclovir affected relapse of KS lesions in a clinical trial of HIV-tainted patients and in three vast follow-up studies. In disdain of these empowering results, no change in the number of PBMCs tainted with HHV-8 was found.[54-57] HHV-8 was extremely sensitive to cidofovir when tried in vitro, though HHV-8 was just tolerably delicate to foscarnet and ganciclovir.[58] Consequently, low doses of cidofovir or a high dose of foscarnet or ganciclovir could stifle clinical recurrence of HHV-8.[59-61] These antiviral medications did not repress episomal virus DNA polymerase, proposing that the inactive type of viral DNA is duplicated by host DNA polymerase.[62] Foscarnet is known to be extremely poisonous, and consequently, clinical dosage for this medication must be controlled for every patient.[63] In spite of the fact that acyclovir has been exceptionally effective in avoiding EBV (gamma-1 herpes virus) disease of oral hairy leukoplakia in AIDS patients, it has demonstrated no such viability against HHV-8.[64-65] Since these medications deal with the level of the viral polymerase, they are viable just in battling effectively reproducing virus and have no impact on the latent phase of infection. While the latent virus is not liable to bring harm, individuals at danger for virus reactivation, , for example, AIDS patients, ought to be checked so that viable treatment can be established if the virus gets to be dynamic.[66-70]

The impact of antiretroviral treatment and the utilization of zidovudine to avoid perinatal transmission were likewise reported.[71] Scientist have demonstrated that one AIDS subject with KS had a low viral load in KS skin lesions and PBMCs while on profoundly HAART treatment, recommending a solid relationship between tumor and HHV-8 viral load despite HAART's having no direct anti HHV-8 action.[72] Antitumor action of fractionated doses of oral etoposide in the treatment of AIDS-related KS was reported with a noteworthy diminishment in KS at a reasonable clinical toxicity of the medication.[73]

The combination of HAART triple-drug treatment has connected with an abatement in the rate of AIDS-related KS. Scientists have contemplated AIDS-KS patients after they had been put on the HAART regimen.[74-75] Diminishment in anti ORF-65 antibody related with clinical changes, yet LNA demonstrated a variable form. Reduce in plasma HIV-1 RNA levels and an increment in CD4 lymphocytes because of antiviral treatment with nucleotide analogs and protease inhibitors related with a relapse of KS lesions.[76-78]

Another antiviral treatment of HIV-1 likewise had an ameliorative impact on AIDS-related KS.[79] Topical treatment with 10% docosanel cream restrains an broad range of encompassed virus in vitro, including herpes simplex virus type 1 and 2, cytomegalovirus, HHV-6, and HIV-1; KS lesions were diminished by 20%, and no treated patients experienced KS illness progression. In this clinical study, no endeavor was made to measure HHV-8.[80-82]

Closing Remarks

The quest for antiviral medications has been fraught by the way that no completely tolerant cell line has been discovered so that biological tests can be led. HHV-8 will contaminate microvascular endothelial cells, yet most research facilities have not observed these cells suitable to work with. Whereas, numerous serological tests have been produced with different degrees of sensitivity and specificity, however no test has yet been developed that identifies both lytic and dormant antibodies in one assay. Moreover, most research facilities appear to lean toward to utilize their own in house testing systems, so that there is, so far, no general agreement on which testing strategies are best. Better and more extensive testing systems are being produced, and these may utilize a blend of antigens made of recombinant proteins.

The future for HHV-8 research is brilliant. In the couple of years since its discovery, a considerable measure has been learned about its complex biology, its relationship with infection, and the function of some of its novel genes. These novel genes incorporate some that will be expressed amid dormancy, such as D-type cyclin homologue, LANA-1 and LANA-2 (vIRF-3), Kaposin and vFLIP. Different genes will be expressed as early lytic genes, and by a variable extent of inactively tainted cells, including vIL-6, other viral homologues of interferon regulatory factor (K9 and K11.1), K1, K15 (LAMP), and vGPCR. Numerous functional and basic lytic genes have been portrayed, as ORF-50, ORF-65, and ORF-K8.1. Vital reagents, including monoclonal antibodies, have been developed for a few of these virally encoded proteins. Just time will tell what applications will be derived from this important research and how it will advantage patients who will be at risk for developing HHV-8-related disease.

KSHV shows that viral immune evasion is personally interlaced with viral oncogenesis. An extensive part of the nonstructural administrative homologs encoded by KSHV instigate cell multiplication additionally target pathways prompting development of adaptive and innate

immunity. Immune system and tumor suppressor signaling are just somewhat overlapping, and different virus equipped for determined contamination without tumorigenesis may have effectively evolved method for repressing resistance without annulling tumor suppressor checkpoints. While the strategies utilized by KSHV and related rhadinoviruses to target cell regulatory pathways are interesting, the lessons gained from these infections can be connected to comprehension random infections, which confront the test of tainting the unfriendly environment of the eukaryotic cell.

Since the pervasiveness of HHV-8 in the overall public is truly low however HIV-1-tainted people will be at a higher risk for developing HHV-8-related malignancies, would an antibody be helpful for those at danger?

Conflicts of Interest Statement

The Authors declare no conflicts of interest.

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