

Human Herpesvirus-8 and Kaposi Sarcoma After Kidney Transplantation

Mechanisms of Tumor Genesis

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Human herpesviruses (HHVs) are able to escape from complete clearance by the immune system. Their ability to become latent is due to their delicate interferences with the immune system. This characteristic makes some of them known as important tumor viruses. Based on the prevalence of the seropositivity for the HHV-8, the world can be divided into 4 regions, one of which is the Middle East with a seroprevalence of 5% to 20%. The incidence of iatrogenic Kaposi sarcoma, a cancer linked with HHV-8 following organ transplantation, is 500 times higher than that in general population. In the Middle East, Kaposi sarcoma is the most common malignancy reported in kidney transplant recipients. In an immunocompromised host, the primary infection with HHV-8 presents with fever, hepatosplenomegaly, lymphoid hyperplasia, pancytopenia, and liver dysfunction. Occasionally, rapid-onset Kaposi sarcoma develops in association with apparent primary HHV-8 infection. In this article, the tumor genesis mechanism of HHV-8 in kidney transplant recipients was reviewed.

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INTRODUCTION

Herpesviruses are very clever viruses that not only present diversely as primary infections, which are sometimes severe and confusing, but also are able to escape from complete clearance by the immune system. Their ability to become latent is due to their delicate interferences with the immune system, such as secretion of viral interleukin (IL)-10 by Epstein-Barr viruses or blocking dendritic cell maturation by cytomegaloviruses. This characteristic makes some of them known as important tumor viruses. Herpesviridae are a family of double-stranded DNA viruses that comprises 3 main subfamilies: alphaherpesviruses, betaherpesviruses, and gammaherpesviruses. Alphaherpesviruses consist of human herpesvirus-1 (HHV-1), HHV-2 (genital herpes virus), and HHV-3 (varicella-zoster virus). Betaherpesviruses also have 3 species. Human herpesvirus-5, namely cytomegalovirus, is one species with both direct and indirect effects on graft and patient survival

after organ transplantation. The other 2 members of betaherpesviruses are HHV-6 and HHV-7 that are the causes of exanthema subitum during infancy and childhood. Further, these viruses may present after organ transplantation with fever, rash, encephalitis, hepatitis, and myelosuppression.¹ The subfamily of gammaviruses consists of 2 species: HHV-4 (Epstein-Barr virus), which is associated with lymphoproliferative disorders after organ transplantation, and HHV-8 or Kaposi sarcoma herpesvirus.²

Exposure to these viruses is quite common. Seropositivity for HHV-1 is about 70% to 90% prevalent in general population, and almost all adults in general population are seropositive for HHV-6 and HHV-7. Based on seropositivity for HHV-8, the world can be divided into 4 regions²⁻⁶: (1) those areas with seroprevalence of less than 5%, including North America, northern parts of Europe, and Japan; (2) areas with seroprevalence of 5% to 20%, such as the Middle East; (3) areas with

seroprevalence of 20% to 40%, such as southern Italy; and (4) areas where seroprevalence is more than 40%, which includes sub-Saharan Africa and Amazon. Among these regions, there are some subpopulations in which seropositivity for HHV-8 is different. For example, in the United States, 15% to 20% of homosexual men negative for and 40% of those positive for human immunodeficiency virus (HIV) are seropositive for HHV-8. Seropositivity is associated with the number of sexual partners and history of sexually transmitted diseases in these areas.⁷ It seems in areas with low seroprevalence, sexual transmission is the major transmission route. Whereas in areas with a high prevalence, the major route of transmission is saliva. In the setting of organ transplantation, transmission from an organ of a seropositive donor to the recipient has been reported.⁸

KAPOSI SARCOMA

Kaposi sarcoma (KS) was first described in 1872 by Kaposi, a Hungarian dermatologist, as a progressive sarcoma.⁹ There are 4 clinical settings in which KS will appear^{2,10,11}: classic, endemic, epidemic, and iatrogenic. Classic KS typically presents in elderly men of Southern-Eastern Europe, has a chronic and indolent course, and may even spontaneously disappear. The endemic (African) type presents in 3 different pictures: (1) more slowly progressing, (2) aggressive cutaneous presentation with frequent visceral involvement that is fatal in 5 to 7 years, and (3) very aggressive lymphadenopathic in young children. Epidemic or acquired immune deficiency syndrome-associated KS is the most common malignancy in patients with acquired immune deficiency syndrome, and its incidence is 20 000 times higher than that in general population.⁶ Indeed, KS is the most common cancer in some parts of Africa where seropositivity of HIV and HHV-8 are both high.⁶

The incidence of iatrogenic KS, which develops after organ transplantation, is 500 times higher than that in general population.¹⁰ The incidence of KS in this group depends on the seropositivity of the population. In the United States, KS represents 5.7% of malignancies in kidney transplant patients (excluding skin cancer), 3% in kidney recipients receiving azathioprine (Cincinnati transplant tumor registry), and 10% in those with cyclosporine-based immunosuppressive regimens. In contrast,

KS is the most common malignancy reported in most series from the Middle East.^{4,12} In a review of 7939 kidney transplant patients in Iran, 55 cases of KS were found that comprised 34% of all malignancies in the study group.¹³ Prevalence of KS may be even higher in liver transplantation in comparison with heart or kidney transplants, and also it seems visceral involvement is less common in kidney transplant patients compared to liver or heart transplant patients.¹⁴

In 1994, Chang discovered the genome of HHV-8 in KS tumoral cells,¹⁵ and later on, the genome was found in all 4 types of KS.¹⁶ The primary infection with HHV-8 in an immunocompetent host is usually asymptomatic or occasionally presents with transient febrile maculopapular rashes; however, in an immunocompromised host, the primary infection may present as fever, hepatosplenomegaly, lymphoid hyperplasia, pancytopenia, and liver dysfunction (hemophagocytic syndrome).¹ Occasionally, rapid-onset KS has been described in association with apparent primary HHV-8 infection.¹⁷

Primarily, HHV-8 can present with KS, body cavity-based lymphoma, primary effusion lymphoma, or plasma cell variant of multicentric Castleman disease.² In all these clinical settings, infection by HHV-8 is necessary but not sufficient. In kidney transplantation, the risk of posttransplant KS is 23% to 28% in seropositive recipients in a period of 3 to 5 years, which is much higher when compared to the classic form of KS.¹⁸ In a study performed in West Azarbayjan of Iran, 25% of kidney transplant recipients were seropositive. In that study, 47% of the patients older than 55 years were seropositive compared to 20% of younger patients. Kaposi sarcoma developed in 4% of seropositive patients in a 16 months follow-up.¹⁸

MECHANISMS OF TUMOR GENESIS

The incidence of most solid tumors increases dramatically following transplantation, except for prostate, lung, and colorectal cancers that increase modestly compared to those in general population.¹⁹ But, is KS a true Sarcoma? There is evidence that KS, at least in its early stages, is not a monoclonal tumor. It can be called an unusual malignancy, resembling hyperplastic angioproliferative lesions with inflammatory changes rather than a true sarcoma.²⁰ As the mechanistic interferences of HHV-8 in producing these tumoral lesions

becomes more clear, the chance of definite cure will increase. Human herpesvirus-8 enters the cell by 2 glycoproteins called *gp* and *gp8.1*.²¹ *Gp* binds to glycosaminoglycans and integrin alpha3beta1, and *gp8.1* binds to heparan sulfate.²² After entering the cell, the virus will interfere with different pathways some of which are critically important in the process of cell proliferation like cyclins, cyclin-dependent kinases (CDK), phosphatidyl inositol-3 kinase (PI3K), and Akt pathways.

Human herpesvirus-8 is a double-stranded DNA virus with a 165-kb pair genome. It has 90 open reading frames. Those genes that are specific for HHV-8 are prefixed with *K* (eg, *K1* to *K15*). Human herpesvirus-8 is famous for "molecular piracy" that is the ability of the virus to produce proteins that are quite similar to human proteins but with different functions such as production of viral IL-6 or viral macrophage inflammatory proteins. By this capability, HHV-8 is able to control key aspects of cell regulation, allowing the cell to replicate, to prevent cell death, and to shut off immune responses in infected cells, corresponding to the strategy of "live and let live." The Table summarizes important viral products and their functions.

Viral Interleukin-6

Viral IL-6, which is encoded by *K2*, is expressed both in replicative and latency phases. This protein is mitogenic via involvement of mitogen-activated protein kinase and signal transducer and activator of transcription signaling pathways, and it is also angiogenic via vascular endothelial growth factor (VEGF) induction. Human IL-6 must first bind to IL-6 receptor alpha (*gp80*), and then it can become

heterodimerized with gp130 in order to transduce intracellular signals that are cell proliferation, anti-apoptotic signals, and acute phase responses. Interleukin-6 signaling is mediated by Jak1/Jak2/Tyk and signal transducer and transcription 3 activator.²³ Interferon-alpha blocks the proliferative and anti-apoptotic effects of IL-6 by decreasing the expression of *gp80*. In contrast, viral IL-6 can directly bind to gp130, and the proliferative effects of IL-6 cannot be blocked by interferon-alpha.^{5,7,24} Viral IL-6 is expressed regularly in plasmoblast of multicentric Castleman disease, in a minority of primary effusion lymphoma cells, and rarely in KS lesions.

Viral Cyclin

Cyclins and CDK have major roles in controlling cell cycle. There are different cyclins, classified as cyclin A to cyclin J, and different CDKs (from 1 to 9). Cyclin D2 along with CDK4, 6-phosphorylate, and inactivation. Inactivation of retinoblastoma protein will lead to progression of cell cycle from the G1 to the S phase. There are some inhibitors of CDK (CDK1) like p16, p21, p15, p27 that are able to block cell cycle progression. Moreover, p53 can block cell cycle progression by increasing synthesis of CDK inhibitors such as p21.

Viral cyclin resembles human cyclin D2, but its activity cannot be inhibited by CDK1 p21 cip1 and p27 kip1. Hence, there may be a trend of cell cycle progression in virally infected cells. Moreover, when the KS tumoral tissues are examined by immunohistochemistry methods, the expression of cyclin is high in KS lesions, which suggests an important role for viral cyclins in the tumor genesis of these lesions.²⁴⁻²⁶ Other viral products, for

Human Herpesvirus-8 Products and Their Functions

Viral Product	Encoding Gene	Function
Viral macrophage inflammatory proteins	<i>K6, K4, K4.1</i>	Blocking mobilization of the antiviral responses of th1
Viral interferon regulatory factors	<i>K9, K10.5</i>	Downregulation of production of interferon-alpha and interferon-beta and expression of p21, interaction with p53
Viral interleukin-6	<i>K2</i>	Constitutively activation of interleukin-6 signaling
<i>K5</i>	<i>K5</i>	Downregulation of MHC class I and ICAM-1 and B7-1
<i>K3</i>	<i>K3</i>	Ubiquitination of MHC I after endoplasmic reticulum export
Viral interleukin-8 receptor	<i>ORF74</i>	Cell proliferation
Viral flip	<i>ORF71</i>	Blocking clearance of virally infected cells by natural killer cells
Viral cyclin	<i>ORF72</i>	Cell proliferation
Latency-associated nuclear antigen	<i>ORF73</i>	Repression of p53 transcriptional activity

*MHC indicates major histocompatibility complex; ORF, open reading frame; and ICAM, intercellular adhesion molecule 1.

example, the latency-associated nuclear antigen and viral interferon regulatory factor-1, also interfere with cell cycle. Latency-associated nuclear antigen binds to retinoblastoma protein in the pocket region, freeing a gene regulatory protein, E2F, which results in cell cycle progression. Further, latency-associated nuclear antigen has a repressive role in p53 transcriptional activity.^{6,27} Viral interferon regulatory factor-1 inhibits transcriptional activation of p53 and impairs p53 stability.²⁸ On the other hand, viral interferon regulatory factor blocks interferon-mediated p21 induction.⁵

Viral G Protein-Coupled Receptor

Viral G protein-coupled receptor (GPCR), which is encoded by the open reading frame 74, has recently been found to have an essential role in genesis of KS lesions. Indeed, it is the only gene that causes transfected mice present lesions quite similar to human KS.^{29,30} Viral GPCR signals through PI3K-Akt pathways and finally results in cell proliferation.³¹ Akt results in tuberous sclerosis complex-2 (TSC-2) inactivation by phosphorylating TSC-2. Consequently, TSC-2 inactivation leads to mammalian target of rapamycin (m-TOR) activation. Activation of m-TOR is mediated by Rheb. Tuberous sclerosis complex-2 is a negative regulator of Rheb. Phosphorylation of TSC-2 by Akt results in the activation of Rheb, thereby promoting the accumulation of active Rheb-GTP and the induction of m-TOR. Activation of mammalian target of rapamycin leads to phosphorylation of p70S6 kinase (key regulator of cellular translation machinery) and eukaryotic initiation factor 4 E binding protein 1. These changes finally lead to overexpression of hypoxia inducible factor, VEGF, and cell proliferation.³¹⁻³³

Viral GPCR is a lytic gene and is only expressed in 10% of KS tumoral lesions. On the other hand, examining the KS tissue by immunohistochemistry reveals overexpression of Akt, p70S6 kinase and VEGF in a majority of tumoral cells, suggesting a paracrine role for viral GPCR, which may explain polyclonality of KS lesions at least in early phases.^{5,24,29,31,34} Alternatively, dysregulated expression of viral GPCR in nonlytic cells may explain initiation of sarcomagenesis. The HIV tat protein and inflammation are two dysregulating factors. Moreover, it may be a reason why antiviral drug ganciclovir that is effective against lytic cells

cannot regress KS lesions.³⁵

In recent years, there is increasing body of evidence regarding regression of KS lesions by sirolimus after transplantation. Hence, there is a link between immunosuppression and antitumor effects.^{30,36} This effect is due to inhibitory activity of sirolimus against m-TOR.^{37,38} In fact, sirolimus decreases not only the risk of KS, but also the overall risk of cancer after organ transplantation. This can be explained by the critical role of PI3K-Akt-m-TOR pathway in pathogenesis of different kinds of malignancies.³⁹ On the other hand, the regressive role of interferon-alpha in the treatment of KS can be explained more clearly by its antiangiogenic effects that are secondary to decreasing VEGF expression by interferon-alpha. There may also be more promising data in the future regarding utilization of drugs that interfere with viral GPCR and its downstream pathways like blockade of VEGF.⁴⁰

Why not all Human Herpesvirus-8-Positive Patients Develop Kaposi Sarcoma?

In fact the answer is not clear, but there are some explanations that may have an impact on the incidence of KS. Genetics may play an important role. Kaposi sarcoma has been associated with human leukocyte antigens DR5, A1, and A2 and inversely associated with human leukocyte antigen B14.⁴¹ In a study that evaluated the association of KS with common variants in genes that modulate host immunity, the risk of development of KS was increased with some polymorphism in IL-13 or decreased with specific polymorphism in human IL-8R.⁴² Moreover, there is a significant positive association between IL-6 promotor polymorphism and the lifetime risk of development of KS in men infected with HIV.⁴³ There are many candidates such as phosphatase and tensin homolog, AKt, or m-TOR that subtle changes in their activities may have a defining role in the risk of development of KS. Sex also may have an influence on the incidence of KS, as KS is more frequent in men despite similar seroprevalence.

Most of cases of KS develop in the context of HIV-1 infection. Indeed, the risk of development of KS in HIV-1-infected patients is 10 times more than that in the HIV-2-infected. The reason seems to be due to production of HIV-1 tat protein that facilitates tumor formation.^{5,44} Further, there may

be another sexually transmissible agent that may have a permissive role in development of KS that may explain why 21% of HIV-positive homosexual and bisexual men developed KS in comparison with 1% of the HIV-positive hemophiliac.⁴⁵ The other factor that can be important in tumor formation is HHV-8 viral load.⁴⁶ In a study done by Engels and colleagues on HIV-positive patients,⁴⁷ HHV-8 viremia was associated with increased risk of KS (odds ratio, 11.7; 95% confidence interval, 1.8 to 76), which means among seropositive subjects, KS incidence was 10-fold higher in those with viremia. Campbell and colleagues⁴⁸ studied the relationship of HHV-8 peripheral blood viral load and KS clinical stage. They found a positive correlation between clinical stage and blood viral load. The median values of peripheral blood mononuclear cell HHV-8 DNA were less than 5 copies per micrograms of peripheral blood mononuclear cell DNA for HHV-8-infected subjects without KS, 6 copies per micrograms for subjects with stage III, and 479 copies per micrograms for those with stage IV.

The other factor that may have an important role in tumor genesis is the intensity of immunosuppression and specific drugs. For instance, the risk of KS after introducing calcineurin inhibitors increased significantly, or sirolimus is associated with decreased risk of KS or regression of tumors. Finally there are different subtypes of HHV-8 virus.⁵ Subtypes A and C are more prevalent in Europe, or subtype Z in common in Zambia and subtype F in Uganda. There may be some differences in the capability of tumor formation among these subtypes. In a study by Mancuso and coworkers, it was found that subtype A KS herpesvirus was almost exclusively present in patients with fast progression of the disease, while subtype C was mainly seen in slow-progressing patients. Also, detection of subtype A was associated with higher blood viral loads.¹⁷

CONFLICT OF INTEREST

None declared.

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