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Kaposi's Sarcoma Herpesvirus: twenty years after its discovery

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Abstract. – Twenty years after the discovery of Kaposi's Sarcoma Herpes Virus (KSHV), many aspects of the pathogenesis have been discovered and innovative approaches are presently applied to the diagnosis and treatment of KSHV associated diseases. The virus is coupled to different types of cancers, as well as to syndromes combined with increased inflammatory response or with immunoreconstitution in immunocompromised hosts. The etiopathological diagnosis of KSHV associated cancers relies on the demonstration of the virus in tumor samples, as well as in the peripheral blood of infected subjects. Novel treatment strategies related to the pathogenetic events of KSHV associated diseases have been recently studied, that are based on drugs able to induce oncolysis by promoting a viral lytic phase or on the blockade of v-IL6, a cytokine with tumor promoting activities. In addition, antiangiogenetic strategies have also been applied to treat KSHV associated cancers. Despite these important discoveries, some aspects of KSHV associated diseases are presently not completely clear and, consequently, response to treatment strategies is still suboptimal.

Key Words
KSHV, Kaposi's sarcoma, Lymphoproliferative disorders, Pathogenesis, Therapy.

Introduction

KSHV was discovered in 1994 by Chang and Moore[1] by representational difference analysis using tissues from patients with HIV-associated Kaposi's sarcoma. In fact the incidence rates of this tumor markedly increased with the onset of AIDS epidemic and this correlation suggested that an infectious agent may have a role[2]. After this initial discovery, other diseases or pathological conditions have been associated with KSHV, such as Primary Effusion Lymphoma (PEL), and Multicentric Castleman's Disease (MCD)[3-8]. Concomitantly the characteristics of the virus, its prevalence in various countries and the mechanisms underlying the development of KSHV associated pathologies have been studied and partially clarified[4,9,10]. In particular, in the last few years this virus has been associated with non-neoplastic conditions linked to acute inflammatory or immunoreconstitution syndromes[4,6]. Thus, the pathogenetic, diagnostic and clinical aspects of KSHV associated disease are becoming more complex. Twenty years after the discovery of the virus, the scientific community has gained much information, sometimes contrasting, on this virus and on the associated pathological conditions. The aim of this review is to describe the most relevant discoveries concerning the virological, pathogenetic and clinical characteristics of KSHV and of its associated diseases. These discoveries have made a relevant positive impact on patients affected by KSHV related diseases.

The Virus

KSHV belongs to the Herpesviridae, a family of double-stranded DNA viruses that includes important human pathogens such as the Epstein Barr Virus, Cytomegalovirus and Herpes simplex-varicella zoster viruses[9]. The KSHV virion has an icosahaedral capsid that is surrounded by a lipid envelope containing several glycoproteins that exert essential activities for the viral life cycle, in particular mediate fusion between the virus and target cells[4,12]. Like other Herpesviruses, KSHV requires an intimate contact for transmission but, differently from Epstein Barr Virus (EBV) or CMV, this virus does not show a widespread diffusion among the general population[6,13,14]. Primary infection probably occurs via saliva through close contacts, and this type of transmission may be important in geographic areas, such as subsaharian Africa, where KSHV

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prevalence reaches 50%[14]. In addition, the virus may be transmitted by blood and blood products including KSHV infected mononuclear cells, solid organ donation and sexual contacts, while transmission directly from a pregnant woman to her fetus appears to be rare[4,6]. In Western countries the prevalence of KSHV is low in the general population (less than 10%) and higher in HIV-infected subjects and men who have sex with men[6,15]. Like other herpesviruses, KSHV can infect lymphoid cells and establish a latent reservoir. However, KSHV infects also non lymphoid cells, such as cells of the endothelial lineage and monocytes. After the entry, the virus establishes a latent phase within the cell, characterized by the expression of a very limited repertoire of genes, including LANA, vCyclin, vFLIP and kaposin[4-6]. LANA blocks TGF-beta signaling and inhibit p53, impairing apoptosis and increasing cell proliferation and survival[16], while vFLIP inhibits death receptor signals by interfering with FAS associated death domain and caspase-8[17]. The conversion into the lytic phase, that is uncommon *in vivo*, results in the expression of all viral genes, followed by viral replication, virion assembly and release of virions from the infected cell. During the lytic phase all KSHV genes are expressed and a number of the proteins codified by these genes have important roles in promoting oncogenesis. In particular, the K1 is a multifunctional protein that activates multiple signaling pathways involved in cellular growth, and viral interleukin 6 (v-IL6) is a cytokine sharing consistent similarities with human IL6. v-IL6 has transforming capacities, induces cellular proliferation and has neoangiogenetic properties[4,9]. B lymphocytes are considered an essential site of viral latency, that can promote dissemination throughout the body. Endothelial cells are a second site of viral latency; they do not appear to establish a long-term viral reservoir, but infection of endothelial cells is the essential primary event giving rise to Kaposi's Sarcoma (KS) development.

Immune Control of KSHV

Immune control against herpes viral infections relies mostly on cytotoxic T cells recognizing specific viral epitopes on infected cells. Studies on viral epitopes and on immune control mechanisms related to KSHV are still incomplete, but it has been clearly established that patients with various KSHV related cancers have different defects in immune control. Furthermore, since many KSHV related cancers develop in HIV-coinfected subjects, immunological data are confounded by the coexistence of the immune compromise related to HIV and/or by the effects of ongoing antiretroviral therapies[18]. Guihot et al[19,20] studied the KSHV specific immune response in subjects with Kaposi's sarcoma and MCD. By using Enzyme-Linked ImmunoSpot antigens of the lytic and latent viral phases, these authors found that few KS patients had an immunological response with low intensity. On the contrary, MCD patients had the same KSHV specific response as compared to healthy subjects infected with this virus[20]. These experimental data may suggest that a reduction of the specific immune response may be responsible for viral proliferation and the development of KS, while the pathogenetic mechanism of MCD does probably not depend on absent or dysfunctional immunity. PEL represents a different entity, since is a tumor arising in subjects with almost no residual immune response, although tumor microenvironment contributes to tumorigenesis, in particular by the production of cytokines[21].

KSHV Associated Diseases

KSHV is the etiological agent of several cancer types as well as of two non neoplastic syndromes (Table I). Kaposi's Sarcoma is the prototypical cancer type related to KSHV, because the virus has been isolated primarily from tissues of patients affected by KS. There are four distinct variants of KS: the classic type, more prevalent among Mediterranean elderly men, the African endemic form, occurring primarily in young black men, the iatrogenic form associated with immunosuppression after organ transplantation, and the epidemic form associated with HIV infection[4,10,22-24]. All these forms have common virological, histological and clinical features, but are epidemiologically distinct. Furthermore, KSHV is associated with several lymphoproliferative disorders. PEL was recognized as a distinct entity after the discovery of KSHV[25]. PEL is a rare B-cell neoplasm which is characterized by a consistent KSHV infection of the tumor clone and typically tends to remain localized to serous body cavities and diffusely spreads along serous membranes[25]. The spectrum of KSHV associated PEL is greater than originally appreciated and includes extracavitary KSHV associated solid lymphoma[3,26]. Extracavitary KSHV associated solid lymphoma (solid PEL) without serous effusions[27] involves mainly extranodal tissues. Apart from their clinical presentation, solid PEL is virtually

identical morphologically, immunophenotypically, and genetically to classic PEL. Tumor cell appearance can range from large cells showing anaplastic morphology to large cells with immunoblastic or plasmablastic morphology. Usually PEL shows features bridging immunoblastic and anaplastic large-cell lymphomas, and frequently displays a certain degree of plasma cell differentiation. Recently, an early variant of solid PEL has been reported. It may occur, though infrequently, as a germinocentric solid microlymphoma[28]. In addition to PEL and its solid extracavitary variants[25], which are by definition KSHV-associated lymphomas, the group of KSHV associated lymphoproliferative diseases has been expanded by the identification, in the HIV setting, of cases of KSHV associated MCD. KSHV infected B cells in MCD have a pre-plasma cell phenotype and plasmacytic/plasmablastic morphology[29,30]. Another rare neoplastic lymphoproliferative disorder, namely large B-cell lymphoma arising in KSHV associated MCD has been recently identified[3,31]. It is worth noting that KSHV associated lymphoid disorders are closely linked to HIV infection[3]. In HIV setting solid PEL is often associated with Kaposi sarcoma (KS) or MCD. Only PEL and its variants occurring in the HIV setting are usually associated to EBV infection of the tumor clone in addition to KSHV[27]. Recent studies[4,6] have identified two additional pathological conditions associated with KSHV, the inflammatory cytokine syndrome (KICS) and the immune reconstitution inflammatory syndrome (IRIS). KICS is characterized by systemic inflammatory symptoms in patients who have often KS. These patients have high cytokine levels, including human and viral IL-6 and IL-10[32]. IRIS develops in a small percentage of HIV patients when they start highly active anti retroviral therapy. It has been proposed that IRIS depends on immune response to pathogens when CD4 T-lymphocyte counts rise. Of note, high morbidity is observed in patients with KS and concomitant IRIS[33]. The list of KS associated diseases is reported in Table I. Although KSHV has been putatively associated with the development of multiple myeloma[34], detailed seroepidemiological analysis failed to demonstrate such an association[35].

Pathogenesis of KSHV Associated Diseases

The expression of a distinct set of KSHV-encoded proteins is currently believed to contribute to PEL pathogenesis. In particular, KSHV encodes for a viral homologue of FLICE inhibitory protein (vFLIP), a potent activator of the NF-κB pathway essential for the survival of PEL cells. Viral IL-6 (vIL-6) is an additional product of KSHV expressed in latently infected cells and to a higher degree during viral replication. PEL effusions usually contain vIL-6 at high concentrations. Since vIL-6 induces vascular endothelial growth factor, vIL-6 likely contributes to angiogenesis, vascular permeability and formation of PEL effusions[9]. KSHV also encodes LANA, a protein able to antagonize p53 and Rb function. In particular, it has been shown that the LANA/p53/mdm2 complex is crucial for PEL cell survival[36]. LANA also sequesters GSK-3 beta thereby stabilizing beta-catenin as well as c-MYC, and activates c-MYC-dependent transcription by promoting its phosphorylation. More recently, LANA was also shown to recruit the p53-related nuclear transcription factor p73, which influences cellular processes like DNA damage response, cell cycle progression and apoptosis[37]. Another KSHV-encoded protein able to interfere with p53-induced transcription is vIRF3/LANA-2. Recent evidence indicates that some of the two dozen microRNAs (miRs) encoded by KSHV may also contribute to PEL development. In particular, miR-K12-11 targets mRNAs involved in the regulation of late stages of B-cell differentiation, possibly contributing to the plasmablastic phenotype of PEL cells[37]. Coinfection with different viruses represents a hallmark of several lymphomas of the immunecompromised hosts[3]. In many cases, viruses do not act as bystanders, but actively have synergistic or regulatory effects on carcinogenesis. Viral cooperation is particularly important when herpesviruses are involved, especially KSHV and EBV[38]. Usually the reciprocal relationship between KSHV and EBV is able to promote signaling pathways or influences the balance between the latent and lytic phase of the viral cycle[13-39]. Double-infected PEL cells represent an ideal model to study viral cooperation: in fact it has been demonstrated that several genes from both viruses, such as KSHV-rta and EBV-zta and LMP-1 are in physical contact, although the precise consequences of this proximity is not clear at the moment[13,39]. Another molecular mechanisms involving viral cooperation may be the targeting by both viruses of the NFkB signaling that is constitutively activated in EBV and KSHV positive lymphomas. In addition in dual-infected PEL cell lines viral exosomes have important tumor growth promoting mechanisms. Exosomes are intracellular vesicles able to transfer biological-

ly active molecules[40]. Exosomes containing herpesviral material have synergistic effects on ribosome function, protein synthesis and are able to activate growth promoting signals. Similar experiments have demonstrated that exosomes containing also retroviral material may contribute to disease pathology in AIDS[41]. Finally, several reports[13,39,42] have demonstrated that PEL harboring KSHV and EBV have higher oncogenic potential as compared to non-infected or monoinfected PELs.

KSHV Detection in Clinical Samples

The prevalence of KSHV infection has been established by serological assaying antibody response against the virus. Initially immunofluorescence assays using infected PEL cell lines have been used[43]. In general, latent antigen base assays are less sensitive as compared to lytic antigen based assays[44]. Later on, immunoenzymatic assays and western blots using purified or recombinant antigens have been established[45]. The etiopathological diagnosis of KSHV associated cancers relies on the demonstration of the virus in tumor samples, as well as in the peripheral blood of infected subjects[38,46]. KSHV can be detected by immunohistochemistry on isolated cells or tissues using antibodies against the latency associated nuclear antigen LANA, that is responsible for maintaining the viral episome linked to the host genome[47]. The diagnosis of KS is confirmed by immunohistochemistry for ORF73/LANA, which detects KSHV in practically all splindle cells. The use of LANA depends on the fact that KSHV in tumor cells is in the latent phase, although a proportion of cells in PEL and MCD express also genes of the lytic phase, such as vIL-6. This protein has an important pathogenetic role, but presently its detection is not used for diagnostic purposes[48,49]. KSHV can be also detected by using Polymerase Chain Reaction (PCR) amplification of several viral genes[46]. During KSHV infection, viral DNA can be detected in serum/plasma samples as well as in peripheral blood mononuclear cells[50]. KSHV viremia can be used both for prediction, diagnosis and follow up of KSHV associated diseases. In particular, it has been demonstrated that KSHV viremia is well suited to predict the development of KS in HIV infected subjects and has a prognostic value in KS and lymphoproliferative disorders[51,52].

Table I. KSHV-associated diseases.

Kaposi's sarcoma
Classic
Endemic
Iatrogenic
Epidemic
KSHV-associated PEL and its solid variant
Classic PEL – in the absence of tumor masses
Solid PEL with serous effusion
Solid PEL without serous effusion
MCD-associated large cell lymphoma
MCD
KCIS
IRIS

Abbreviations: KSHV, Kaposi sarcoma-associated herpesvirus; MCD, multicentric Castleman disease; PEL, Primary effusion lymphoma, KCIS, KSHV-associated inflammatory cytokine syndrome; IRIS, Immune reconstitution inflammatory syndrome.

Treatment of KSHV Associated Diseases Based on Pathogenetic Mechanisms

In HIV-infected subjects, treatment of KSHV-associated disease benefits of the treatment of HIV-infection itself[53,54], and standard chemotherapy regimens have been applied to KSHV associated tumors, but these topics are beyond the scope of this review and have been exhaustively examined in the scientific literature[3,22]. We herein will describe only those treatment strategies more related to the pathogenetic events described in the previous sections. An oncolytic approach to treatment has been recently suggested[55]. This treatment is based on the use of bortezomib, that is a potent inducer of KSHV (and EBV) lytic cycle, although its use has been restricted to few cases[55,56]. An additional experimental approach targets neoangiogenesis, that represents a pathogenetic events in KSHV associated diseases. Bortezomib, an angiogenesis inhibitor, has been considered as a potential drug to be used in this context, but clinical data are not available at the moment. Target therapies may benefit of anti CD30 molecules (brentuximab vedotin)[57]. Brentuximab vedotin (SGN-35) is an anti-CD30 monoclonal antibody conjugated to a microtubule-disrupting agent. In vitro treatment of CD30+ PEL cell lines with brentuximab vedotin decreased cell proliferation, induced cell cycle arrest, and triggered apoptosis[57]. Finally, the possibility to block v-IL6, a potent growth factor of KSHV associated cancers, has been recently suggested to treat viral associated tumor proliferation[58]. This drug has been recently approved by US Food and Drug Administration for the treatment of MCD. Recently, the results of a phase II clinical trial have been pub-

lished. All MCD patients in this extension study have received siltuximab for a prolonged duration (up to 7 years) without evidence of cumulative toxicity or treatment discontinuations and with effective disease control[59].

Conclusions

After the discovery of KSHV in 1994, the pathogenesis of KSHV associated diseases extensively investigated and some important aspects have been clarified, which has allowed the definition of diagnostic criteria based on the detection of this virus in infected patients, on the demonstration of viral products within neoplastic cells. The cancerogenic role of this virus has been established based on the demonstration that this virus causes important molecular alterations that ultimately lead to tumor development. Based on these experimental and clinical data, appropriate innovative therapies have been proposed and applied to a limited number of patients. Despite these discoveries, some biological and clinical aspects of KSHV associated diseases are still not clear and further virological, pathological and clinical data are needed to further clarify this matter.

Conflicts of interest

The authors declare no conflicts of interest.

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