**AIDS** Rev. 2010;12:40-51

# Immunological and Inflammatory Features of Kaposi's Sarcoma and Other Kaposi's Sarcoma-Associated Herpesvirus/Human Herpesvirus 8-Associated Neoplasias

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## Abstract

***During the last 15 years, virologic and immunologic studies have provided a series of valuable clues on the modalities of γ-herpesvirus-induced oncogenesis, which do not only consist of the direct subversion of intracellular signaling pathways, leading to a frank neoplastic molecular network in the infected cell, but also rely on viral manipulations of the cellular and cytokine microenvironment, especially in conditions of immunodeficiency in the host. At the virus-host interface, something iniquitous, strikingly favoring the aggressive expansion of human herpesvirus 8-infected lympho-endothelial clones, known as Kaposi's sarcoma, often occurs in different types of immunocompromised patients, able to establish a deleterious "pro-Kaposi's sarcoma" neo-angiogenic inflammatory network. However, these patients may control – or even resolve – the neoplastic burden as soon as an immunologic reassessment restores functional anti-Kaposi's sarcoma immune responses and reconstitutes a proper inflammatory environment. Indeed, the occurrence of iatrogenic Kaposi's sarcoma remissions, after the reduction or switch of immunosuppressive regimens, strongly suggests that the reset of immunologic constraints characterizing the Kaposi's sarcoma onco-pathogenic system may be sufficient to inhibit human herpesvirus 8-positive lympho-endothelial proliferations. Accordingly, immunologic reports all underline the pivotal protective role of anti-human herpesvirus 8 memory T-cells (harmonically, both $CD8^+$ and $CD4^+$ subsets), thus definitely implying a general requirement for an effective, antiviral immuno-inflammatory environment, based on correct and productive interactions between different compartments of dendritic, myeloid, and specific T-cells, in order to achieve and maintain optimal control on human herpesvirus 8-associated antigenic stimulations and Kaposi's sarcoma disease.***

***In this review, we recapitulate some remarkable features about the outstanding immunologic issue raised by human herpesvirus 8-driven neoplastic outgrowths in immunodeficient patients, and in particular, we discuss the emerging view of Kaposi's sarcoma as an atypical neoplastic process, tightly dependent on immune system dynamics. It is conceivable that functional dissection of the specific immune responses, capable to cope with human herpesvirus 8, and further definitions of a global inflammatory profile with protective activity against Kaposi's sarcoma outbreaks, will eventually foster immunologic monitoring protocols during the follow-up of AIDS and posttransplant patients, either preventing or treating human herpesvirus 8-related tumors by multifunctional immunomodulation or prompt development of adoptive immunotherapeutic approaches.*** **(AIDS Rev. 2010;12:40-51)**

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## Key words

***Immunology. Inflammation. HHV-8. Neoplasia. Kaposi's sarcoma.***

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## Introduction

Early after its discovery in 1994[1-3], Kaposi's sarcoma-associated herpesvirus (KSHV), the last identified human herpesvirus (namely HHV8), has joined human papillomavirus (HPV), Epstein-Barr virus (EBV), human T-lymphotropic virus 1 (HTLV-1), and possibly also hepatitis C virus (HCV), in the small group of human viruses which have been assessed to specifically drive oncogenic processes, by directly promoting the neoplastic transformation of infected cells[4-7].

Virus-associated neoplasias have represented a frontline setting to search for antitumor immune defenses, as well as providing the opportunity to detect relevant T-cell responses against cancer cells that bear foreign viral antigens. So far, several lines of research on tumor immunology have prompted a wealth of hints on the complex host-virus interactions, underpinning the emergence of the neoplastic cell network and related clonal expansions, which typically arise as life-threatening diseases in different types of immunodepressed patients[8,9]. As major clinical milestones, besides anticancer vaccination strategies, several reports have shed light on the efficacy of specific cytotoxic T lymphocyte (CTL) therapy to control EBV-related diseases (posttransplant lymphoproliferative disease, Hodgkin's disease, nasopharyngeal carcinoma) as preemptive therapy or at tumor relapse[9-13]. On the contrary, adoptive immunotherapeutic approaches for HHV8-related neoplasias have not yet been so far investigated[14].

In this review, we deal with the immunological data that depict the close intertwining between different HHV8-driven neoplastic proliferations and the specific host immune control, offering some insights into the pathogenic and clinical features of Kaposi's sarcoma (KS) and other HHV8-associated malignancies.

## Kaposi's sarcoma: from pro-Kaposi's sarcoma inflammatory environment to specific immune control

Kaposi's sarcoma was first described in 1872 by Moritz Kaposi as a cutaneous proliferation of "multiple pigmented tumors" in elderly people, particularly from the Mediterranean area, Eastern Europe, and people of Jewish descent[15]. Today, this vascular neoplasia – invariably infected with HHV8 – is better known as a worldwide disease frequently undermining the clinical course of either HIV-coinfected or posttransplant patients, as well as of other patients undergoing immunosuppressive treatments[16]. Confirming the early suggestions deriving from histological observations, iatrogenically immunosuppressed patients have exemplified how KS is a rather unusual neoplasm, representing the prototype of the viral-induced tumor proliferation under fine immunological control, aggressively spreading to skin and visceral sites when immunosuppression prevails, while possibly vanishing to partial or complete clinical regression after the reduction, or change, of immunosuppressive regimens[17]. Moreover, the simultaneous multifocal development of oligoclonal KS tumors well supports the notion that KS is a preferred outcome of HHV8 infection in the permissive immunocompromised host, reflecting also the polyclonal nature of some EBV-associated posttransplant lymphoproliferative diseases (PTLD)[18]. Further confirming a predisposing impairment of the protective immune network against non-self antigens, posttransplant KS cases can even display donor-derived neoplastic clones[19]. By analogy with AIDS-related and iatrogenic clinical forms, the classic and the endemic forms could also be considered as a complex disease, entailing silent conditions of immune impairment. These tumors usually affect HHV8-positive elderly Mediterranean individuals or African children with a layer of predisposing genetic and environmental factors, still largely to be identified, which in turn may result in the cellular environment allowing the virus-driven endothelial outgrowth[20-22].

## Kaposi's sarcoma pathogenetic onset: detrimental immune effect in HHV8-associated cellular milieu

As shown by histopathological analyses on early maculopapular KS skin lesions, it is evident that massive inflammatory infiltrates dominate the initial steps of KS development. While HHV8-infected angiosarcoma cells (the so-called spindle cells) are still rare, different types of immune and endothelial cells crowd into the lesion, and only later, at KS nodular stage, spindle cells eventually prevail[17,23-25]. It has well been noted that, whereas the neo-angiogenic and the inflammatory components are usually revealed only at the late stages of solid tumors as metastatic processes start to take place, on the contrary, in KS, non-neoplastic components seem to causatively precede the over-proliferation of spindle cells in the pre-neoplastic/early-neoplastic lesion[17]. Thus, at the early stages, KS tumors actually appear as a "chronic inflammatory neovascular

disease", mainly characterized by abnormal lympho-endothelial proliferations (the so-called slit-like spaces) and activated lympho-monocytoid infiltrates ($CD8^+$ T-cells along with $CD4^+$ T-cells, activated B-cells and plasma cells, dendritic cells), exceptionally raising even as a Koebner phenomenon[17,23-26].

Anyway, immunological studies have broadly assessed that HHV8-specific T-cell responses are usually lower or totally absent at the time of KS diagnosis, particularly in AIDS and posttransplant clinical forms, while specific immune recoveries have been associated with KS regressions (see Kaposi's sarcoma immune control)[27,28]. In terms of KS pathogenesis, on the host side, all the above observations suggest that HHV8-specific T-cell clones and other functional non-specific immune cells have to be at least ineffective against tumor growth, but likely they even take a fundamental part in the cellular hypoxic environment, producing a particular pro-angiogenic cytokine milieu, strikingly associated with over-proliferation of HHV8-positive lympho-endothelial sarcomatoid cells[29-32]. In brief, KS tumor environments have shown rather low levels of transforming growth factor-beta (TGFβ) versus very high levels of interleukin 6/vascular endothelial growth factor (IL-6/VEGF), plus other inflammatory growth factors, chemokines and interleukins, mainly interferon gamma (IFNγ) and IL-10[33-35]. Consistently, *in vitro* models of KS (spindle cell component), being highly-dependent on cytokine-rich medium derived from supernatants of activated T-cell cultures, are difficult to set up and maintain in long-term cultures, while tumors other than KS are traditionally able to indefinitely proliferate with ease, even in serum-reduced conditions[25]. Interestingly, KS-transplanted cells in an immunodeficient murine model rapidly originate pro-angiogenic inflammation *in situ*, but eventually succumb since a putative host-versus-graft response arises in the engrafted tissue, while conversely, a typical neoplasm is classically defined for its transplantability into nude animals[36].

Functional immunological assays are now required to finely dissect the KS intralesional immune network, to shed further light on the suppression mechanisms of tumor-specific immunity, while different immune cells crowd into the tissue where KS is growing out. Indeed, the general immunosuppressive level may lead to engulf the site of HHV8 replication with plenty of immune cells not primed to eradicate the non-self (viral) antigens, so that the neoplastic proliferation can remain silent to the immune surveillance[37]. Furthermore, inflammatory cells may be decisively misdirected to contribute to the pro-angiogenic milieu supporting KS proliferation. Down into this pro-KS "attractee", clearance failure of HHV8 antigenic burden can *per se* induce mechanisms of immunotolerance allowing KS escape[38].

Concomitantly, on the virus side, spindle cells are invariably associated with the latent form of HHV8 infection, which is able to reprogram the cellular gene network towards the lymphatic endothelial profile by an orchestrated expression of several viral proteins, with known pro-survival/oncogenic potentials in KS: the resultant angio-proliferative phenotype shows a particular self-sustained growth by secretion of autocrine growth factors, mainly VEGF, IL-1β, and IL-6[25,39,40]. In particular, the HHV8-driven lympho-vascular neoplasia takes advantage of the high surface expression of different VEGF-receptors, thus receiving a marked angio-proliferative input from different members of the VEGF family (VEGF-A, C, and D), typically abundant in the inflammatory hypoxic milieu[41,42]. Downstream from VEGFR and other growth factor receptors (epidermal growth factor receptor, fibroblast growth factor receptor), PI3K/Akt/mTOR and mitogen-activated protein kinase (MAPK) signaling systems are abnormally activated to further enforce cell metabolism and growth[43,44]. Among viral oncogenic proteins, latency-associated viral FLICE inhibitory protein (vFLIP) has recently been pointed out to be the pivotal molecular switch for HHV8-induced angiosarcoma genesis, since its expression has been well demonstrated to induce spindle-shape phenotype/metamorphosis in primary lymphatic and vascular endothelial cells, and strikingly contribute to their proinflammatory phenotype (secretion of IL-6, IL-8, RANTES, macrophage inflammatory protein 3α), mainly by activation of nuclear factor kappa B (NFκB)[45]. Moreover, in order to slow down the activation of apoptosis, host p53/ataxia telangiectasia mutated and caspase systems are inhibited during different phases of HHV8 infection, mainly by viral latency-associated nuclear antigen (LANA), viral interferon regulatory factor 3 (vIRF-3) and vFLIP, vCyclin, vBCL2, and K7, respectively, whereas LANA and vIRF-3 can directly cause cMyc deregulation and proliferative rate increase, together converging to the clonal expansion of HHV8-infected cells[16,17].

Anyway, intriguingly, the notion that HHV8 latency program is not sufficient to strongly immortalize spindle cells, as well evidenced by viral episome loss in biopsy-derived cultures, has raised different unsolved scenarios for KS oncogenesis[17,46]. Significantly, even if blood viremia has not yet shown clear-cut correlations either

with KS evolution or specific immune response, some low levels of HHV8 lytic replication are commonly detected during KS disease, claiming its role in the multifactorial process of KS pathogenesis[47]. In the first instance, HHV8 lytic replication can support either *de novo* viral infection of endothelial cells or reinfection of spindle cells that lose HHV8 genome. Interestingly, it has been demonstrated *in vivo* that constitutive signaling from lytic G protein-coupled receptors (vGPCR) can produce high microenvironmental levels of VEGF and other growth factors (IL-6, IL-1β, IL-8), with strong paracrine effects not only on latently infected spindle cells, but also on immune T-cell subsets and neo-angiogenic endothelial cells[46,48]. Consistently, vGPCR transgenic mice developed focal angio-proliferative lesions, resembling KS initiation[49]. Additionally, during the lytic phase, HHV8-infected cells express several CC chemokine analogs (vCCL-1,-2,-3), favoring the expansion and survival of T helper 2 (Th2) lymphocytes and endothelial cells, which become the prevalent cell types of the site of viral replication[17]. The HHV8-infected cells also secrete vIL-6, a viral homolog of IL-6, particularly promoting neo-angiogenesis, while inhibiting I-type IFN receptors[50,51]. Indeed, similarly to other human pathogens, and in particular to human herpesvirus infections, HHV8 can decisively counter the host antiviral immune responses in order to achieve the fundamental immunological escape for its outgrowth[52]: the virus also acts in a specific way either to reduce antigenic stimulation from the infected cell, by downregulating human leukocyte antigens HLA-A, HLA-B, HLA-C (adoptive immunity) and HLA-E (innate immunity), or to decrease antiviral immune activation in monocyte-macrophage and lymphoid subsets by directly manipulating a long series of intercellular interaction molecules, such as host CD1d, CD86, ICAM1, PECAM1, BCR, or viral KCP, vCD200, K15[38].

Since hypoxia-induced mechanisms specifically induce lytic replication, it can be argued that, in particular, hypoxic tissues (such as the skin at distal limbs) may strikingly favor the uncontrolled HHV8 reactivation, leading to the instauration of pro-KS inflammatory microenvironment[53]. Moreover, the detection of specific T-cell responses against HHV8 lytic antigens can sometimes clearly precede the reappraisal of immune responses against HHV8 latency associated proteins, and then clinical KS regression, further supporting a possible link between HHV8 active replication, immune response boosting, and KS evolution[54].

Thus in KS, initially as a vicious immunological feedback, the persistent failure of HHV8 clearance is associated with deleterious modifications in impaired immune functions, which cannot properly express their anti-KS potentials, but fall to participate in the establishment of the fundamental pro-KS angiogenic inflammation, underpinning over-proliferations of HHV8-positive spindle cells (Fig. 1).

## Kaposi's sarcoma immune control: anti-HHV8 T-cell dynamics are associated with Kaposi's sarcoma clinical evolution

In all its clinical forms, KS regression has directly been linked to a general increase in the magnitude of HHV8-specific CD8+ T-cell responses, either versus latent or lytic antigens, as well as to the recovery of innate immune functions (natural killer cell activity)[55-57] (Fig. 2). Even though Th1 memory responses are now considered of primary importance in the control of herpesvirus latent infections and related diseases[58-60], very few data offer hints about HHV8-specific $CD4^+$ T-cells and the putative Th1/Th2 skewing during the different phases of KS course[17,35,61,62]. Anyway, anti-KS $CD8^+$ T-cell responses have been accurately summarized in detail by a recent revision work, which in parallel describes actual knowledge on EBV- and HHV8-specific $CD8^+$ effector T-cells (CTL), mainly streaming from diverse applications of antigen-specific immunoassays (IFNγ-EliSpot, major histocompatibility complex class I tetramer-based flow cytometry) to the definition of functional immunological profiles in peripheral blood mononuclear cell (PBMC) samples from infected patients[55]. By comparison with EBV, immunogenic HHV8 epitopes seem rather more difficult to discover. In cytokine secretion assays, full-length HHV8 proteins (either recombinant or peptide-spanned) have been proposed as a direct source of multiple immunogenic motifs, allowing to bypass the search for single HLA-specific, short or long epitopes, and thus, roughly detecting both antiviral $CD8^+$ (CTL) and $CD4^+$ cytotoxic T-cells (Th1 cells)[54,61,63]. Such immunological monitoring systems could now pave the way for a clinically relevant, "crude screening" of specific T-cell responses against viral tumors[64].

In brief, early reports on HIV-coinfected patients first demonstrated the occurrence of anti-HHV8 CTL cells, which recognized a variety of short epitopes derived from different viral proteins, such as lytic surface glycoproteins K8.1, gH, gB, the processivity factor open reading frame ORF57 and ORF65, as well as latent Kaposin A and ORF73/LANA, consistently showing that peripheral blood HHV8-specific immune responses are

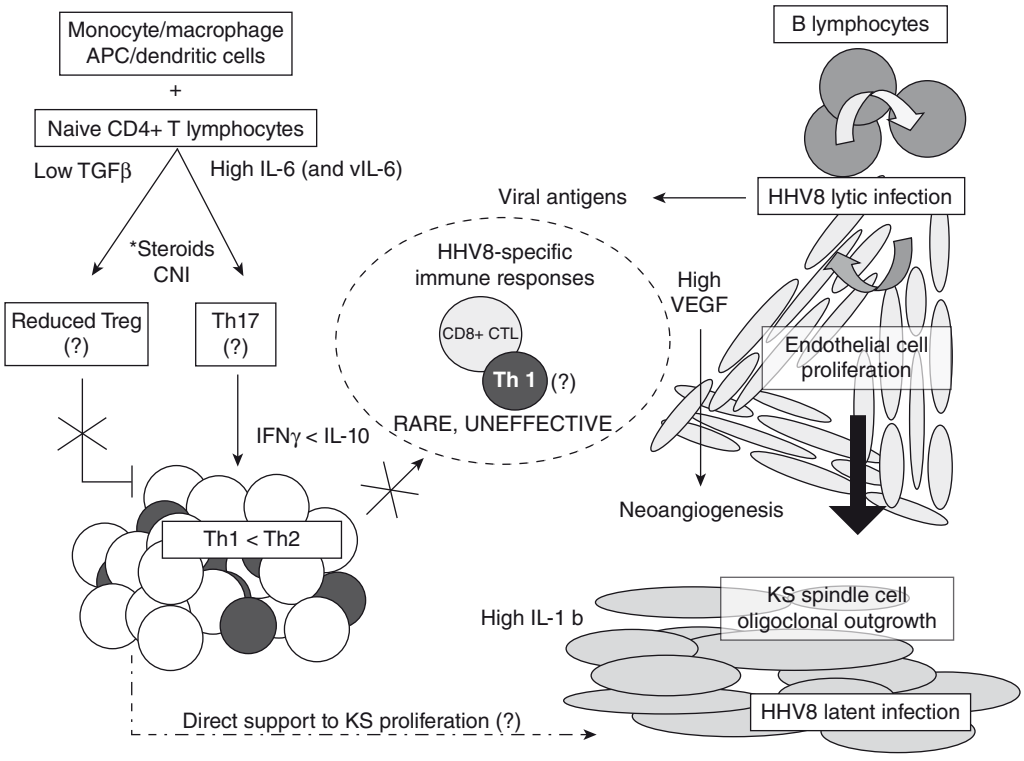


**Figure 1.** *"Pro-KS" inflammatory-neoangiogenic environment. Treg: T regulatory; HHV8: human herpesvirus 8; Th: T helper; CTL: cytotoxic T lymphocyte; VEGF: vascular endothelial growth factor; IL: interleukin; KS: Karposi's sarcoma.*

more frequently associated with primary infection and lytic reactivation phases rather than with viral latency[63,65-75]. However, as with EBV, the anti-latent HHV8 immune surveillance should be enriched in several tissues, especially patrolling lymphoid organs against the emergence of viral-driven neoplasias[55].

Indeed, more recently, KSHV-specific $CD8^+$ T-cell responses (particularly the latent types) have been documented to be low in AIDS and classic KS patients, while, by comparison, the asymptomatic HIV-coinfected group appeared to be protected by higher levels of anti-HHV8 immune defenses; of note, KS cases were specifically lacking all the differentiation steps of effector memory $CD8^+$ T subsets, whereas a number of central memory $CD8^+$ T-cells were still detected[76].

Furthermore, another immunological survey independently showed that patients with different KS forms had significantly less frequent and weaker anti-HHV8 CTL responses (both latent and lytic); in particular, AIDS/KS and posttransplant patients progressing to KS had lower values than matched control groups, represented by HHV8-positive/HIV-positive and transplant recipients without KS[77]. Confirming previous phenotypic analyses, marked differentiation towards perforin-expressing, late effector phenotypes ($CD45RA^+$, $CD27^-$, $CCR7^-$, also known as EMRA T subset) was detected in patients controlling KS disease or HHV8 primary infection[69,77]. Importantly, an absence of HHV8-specific CTL was directly evidenced in KS lesional biopsies from two classic KS patients. In addition, in a single posttransplant KS patient, a time course displayed fine correlations between anti-HHV8 immune dynamics, KS clinical remission/recurrence, and viral loads[77].

In line with this, in a series of posttransplant recipients, anti-HHV8 immune responses were absent at the time of KS diagnosis, but resurfaced after KS remission

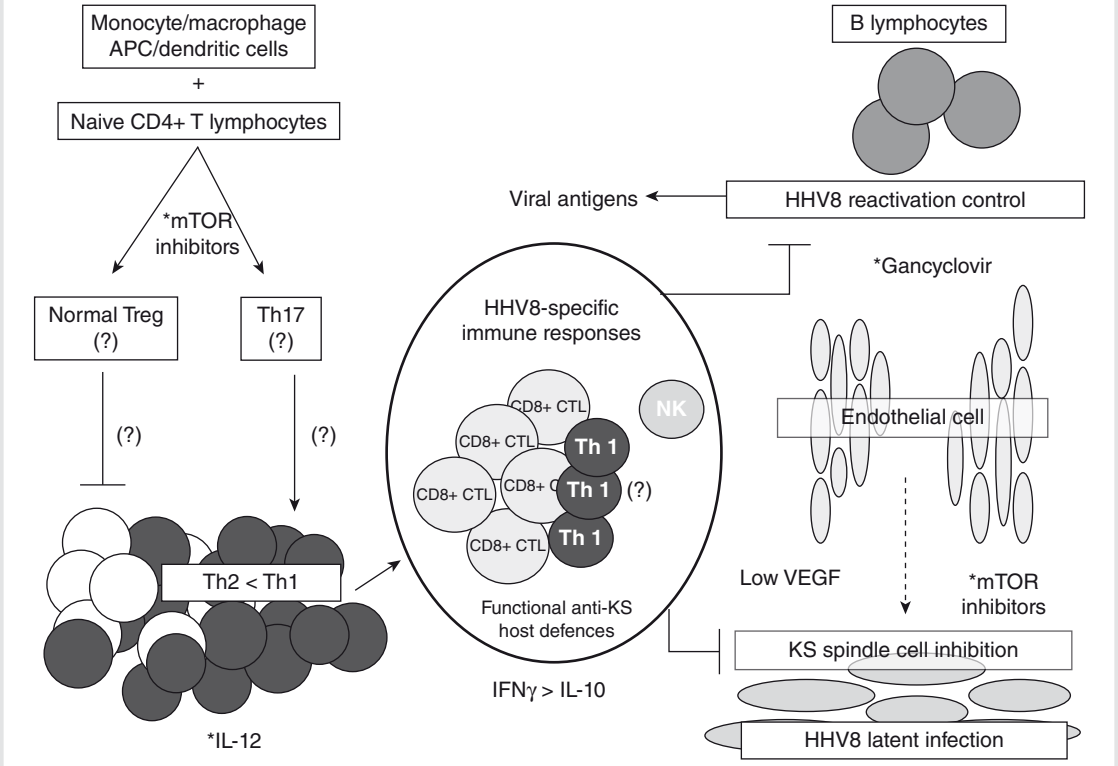


**Figure 2.** *"Anti-Kaposi's sarcoma" immune environment. In theory, whichever strategy is able to disrupt immunological constraints of the Kaposi's sarcoma immuno-pathogenetic system, it should also be expected to contribute to resolution of this atypical "inflammatory" neoplasia. APC: antigen-presenting cell; HHV: human herpesvirus 8: mTOR: mammalian target of rapamycin; Treg: T regulatory; Th: T helper; VEGF: vascular endothelial growth factor; KS: Kaposi's sarcoma; IFN: interferon; IL: interleukin.*

following a reduction of the immunosuppression regimen, even if at lower levels than in HHV8-positive recipients who never developed KS[61]. Moreover, clinical KS regressions, achieved by switch to rapamycin in two posttransplant KS liver recipients, nicely correlated with the recovery and maintenance of both polyfunctional $CD8^+$ and $CD4^+$ effector/central memory responses against HHV8 both lytic (K8.1) and latent (LANA) antigens[61]. On the contrary, failure to achieve a complete tumor regression in another renal transplant patient treated with rapamycin was associated both with the absence of the polyfunctional immune profile related to viral infection control, and with the lack of reappraisal of HHV8-specific $CD4^+$ effector/central memory cells[61]. Thus, it is conceivable that rapamycin, a promising immunosuppressive agent with broad antitumoral activity, while directly killing KS cells by inhibition of the Akt/mTOR axis, may also boost optimal antigen presentation and allow effective antiviral immune recovery without inducing graft rejection[61,78-80].

Altogether, immunological data support the critical role of anti-HHV8 immune surveillance in KS onset and regression in all its clinical forms; however, CTL cell responses have showed variable magnitudes among different KS settings, which is likely dependant on immunological conditions underlying the development of HHV8-related disorders. As shown for other pathogen-induced diseases in immunocompromised hosts, the effort to track specific dynamics of immune T-cells could provide useful clinical information about disease evolution in different clinical settings[81-84].

Iatrogenic KS may also be diagnosed in patients with autoimmune diseases, treated with corticosteroids or other immunosuppressants like calcineurin inhibitors

(CNI), which are well known to induce herpesvirus reactivations, supporting the role for HHV8 replication in the immune deregulation leading to the expansion of latently infected spindle cells[85]. Consistent with this, we reported a case of iatrogenic KS, showing remissions and relapses in dependence with slight modifications of low-dose glucocorticoid treatment, used to control a long-lasting condition of undifferentiated autoimmune arthritis[54]. The contribution of HHV8 replication to KS initiation has also been suggested by a dramatic decline in KS incidence following ganciclovir therapy in AIDS patients[86].

In HIV-positive patients, HAART therapy has also shown to highly impact on AIDS-KS disease, frequently leading to prolonged KS regressions and low KS incidence in several cohorts undergoing different HAART regimens[87,88]. Reasonably, such anti-KS activity of HAART therapy has been attributed to the partial immune reconstitution owing to $CD4^+$ T-cell count recovery, along with the reduction of viral loads; in addition, HAART-induced repression of HIV infection (TAT protein) may directly affect the neovascular outgrowth of spindle cells[88,89]. However, in HIV-positive patients undergoing HAART therapy, KS flares during immune reconstitution inflammatory syndrome (IRIS) further underline the active role of the immune imbalance in KS pathogenesis; the abnormal re-expansion of $CD4^+$ T-cell subsets can sometimes represent a putative leading cause of IRIS-associated autoimmune diseases and KS neoplastic proliferations. Thus, in this view, KS tumor development should not only rely on functional lack of protective HHV8 immunity, but also on dysfunctional immune activities[90-92]. Interestingly, recent advances in the study of immune dynamics describe a new instructive model of T $CD4^+$ subset diversification and plasticity. Briefly, while TGFβ prevalence in the milieu primes autocrine mechanisms for the expansion of T regulatory cells ($T_{reg}$) and suppression of inflammation, on the contrary, IL-6 and IL-1β inhibit TGFβ pathways and preferentially drive the naive cell toward immune-inflammatory T-cell outcomes, and, in particular, to the late-discovered proinflammatory phenotype (Th17 subset), which is now proposed as a principal $CD4^+$ defense against pathogens. Then, if conditions of either IFNγ or IL-10 prevalence occur, the Th17 cells can differentiate, either into the cytotoxic Th1 subset or the allergic/tolerogenic Th2 subset, respectively[93,94]. In KS immunopathology, a skewing to Th2 functions could be sustained by IL-10 overcoming IFNγ effects, as detected in the biopsies[95-97]. Consistent with this possible scenario, glucocorticoids, which are reported to downregulate TGFβ signaling, may act by reducing $T_{reg}$ subsets and promoting a proinflammatory feedback[33]. Of interest, by comparison to CNI immunosuppressive agents, anti-KS mTOR inhibitors are well known to allow the expansion of $T_{reg}$ subsets ($CD4^+$, $CD25^+$, $FOXP3^+$) during posttransplant follow-up, early after initiation of treatment, probably because FOXP3-induced cell proliferation (based on Pim2 pathway) can bypass mTOR functional loss. This event may further contribute to the pleiotropic activities of these immunosuppressive agents against KS by direct suppression of the fallacious immune-inflammatory network sustaining spindle cell proliferations, yet allowing new emergence of proper anti-KS immune responses[80,98]. Indeed, also retinoids, which offered some objectives results against KS, have recently been demonstrated to promote $T_{reg}$ expansion[88,99]. However, to date no data exist about $T_{reg}$ and Th17 populations and some other important cytokines (IL-21, IL-22, IL-23) in KS. Anyway, intralesional administration of IL-12, a cytokine that enhances Th1 immunity inducing IFNγ as well as antiangiogenic effects, is currently in clinical tests as a highly effective co-adjuvant therapy in AIDS-KS[100,101]. So far, *in situ* studies on HHV8-specific T-cells are still too sporadic to permit further speculations on these immune dynamics[77]. Better comprehension of the systemic/local relationship of anti-KS immunity should also offer the opportunity to improve patients' monitoring and treatment of KS disease. On strict comparison, functional analyses of anti-melanoma immunity have already shown an immune movement of $CD8^+$ specific T-cells from the periphery to tumor site, and effector memory (EM) T-cell enrichment is often detected *in situ* during the remission phase, even leading to regression of "in-transit" metastasis[102,103]. Melanoma tumor-infiltrating T lymphocytes are estimated to be about 10-fold more frequent than antitumoral functional cells circulating in peripheral blood[104]. Thus, melanoma experience and innovative technologies for tissutal imaging should prompt further investigations on pathogenic versus protective dynamics at the site of KS neoplastic lesions, in relation with HHV8-specific immunological measurements in peripheral blood and bone marrow samples.

Today, it appears clear that KS is a complex disease, triggered by a variety of viral and host factors rather than one overriding cause. Not least, gene polymorphisms (single nucleotide polymorphisms, SNP) are revealing some subgroups of patients with higher risk for KS development; several IL-6 and other cytokine SNP are statistically associated with different clinical

forms of KS[105,106]. In conclusion, KS proliferations should become easier to be prevented and treated in clinical practice, as soon as we can get further insights about the challenging model of immuno-viral pathogenesis, allowing to disclose rational immunomodulating and antiviral approaches against KS exacerbations.

## HHV8-associated B-cell lymphomas: from viral cell-fate reprogramming to tumoral immune escape

During γ-herpesvirus infection cycles in the B-cell compartment, both EBV and KSHV/HHV8 are well codified to deregulate host cell signaling pathways by a precise expression of latent and lytic viral transcription programs, evolved to manipulate B-cell developmental stages[107,108]. During this harmful process, HHV8 can typically contribute to the pathogenesis of primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD)/plasmablastic lymphoma, not only by a latency program, which supports the aberrant molecular networks of the plasmablastic (pre-terminally differentiated) B-cell neoplastic clones, but also by a lytic program, which induces the cytokine and chemokine factors deregulating the impaired immune functions[109-113]. In particular, HHV8-specific LANA, vFLIP, vGPCR, and vCyclin may increase proliferative rates upon apoptosis, mainly by activating NFκB, PI3-K/Akt/mTOR and MAPK pathways and improving cMYC activity and cell-cycle progression[114]. Interestingly, also viral microRNA, expressed by HHV8 during latency, has been proposed to specifically interfere with germinal center /post-germinal center differentiation stages[115-117]. Mainly, these peculiar B-cell lymphoproliferative disorders affect immunocompromised patients who likely develop an immune-inflammatory network permissive to malignant outgrowth, strikingly failing to eradicate virus-transformed clones as accumulating deleterious genetic lesions[107,118]. Indeed, although the disease sites and the histomorphologic features are largely different between PEL and MCD/plasmablastic lymphoma, in both conditions lymphomagenesis is immunologically linked to high levels of IL-6 (and vIL-6), VEGF, and IL-10, and is allowed as a consequence of the multiple viral strategies for immune evasion against both CTL and NK cells[118-120].

All these viral and immunological mechanisms, and probably other unknown co-factors, meet to set up the environment where HHV8-positive B-cell abortive plasmablasts can proliferate unrestrictedly (Fig. 3). In sharp contrast with the oligoclonal spindle cells of KS, PEL cases are usually characterized by a single selected clone, with several recurrent chromosomal abnormalities, which are the results of the genetic instability, a key-feature of γ-herpesvirus-driven molecular network in the activated B-cells[121]. Thus, PEL lymphomas, frequently also infected with EBV, more closely resemble typical solid neoplasias accumulating different genetic lesions to achieve the required growth advantage and release from tissutal control. Indeed, so far, PEL cell lines derived from patients' neoplastic fluids are the unique *in vitro* models of HHV8-associated neoplasia, ultimately showing a more efficient *in vitro* stabilization of viral latency[122]. Rapamycin was demonstrated to be efficacious against PEL *in vitro* and *in vivo*, by inhibiting the AKT proliferative pathway, even if IL-10 or IL-6 supplementation can bypass mTOR inhibition and related growth arrest[123]. Surprisingly, two posttransplant patients were reported to develop PEL despite being under rapamycin treatment, raising the possibility that the antiproliferative and immunomodulatory effects of rapamycin may not be clinically so relevant in this lymphoproliferative context[124]. Indeed, also HAART treatments, while highly effective against KS disease, failed to show similar results in the MCD setting. The incidence of MCD showed a statistical increase over time during the HAART era, with an emerging association between well-preserved immune functions (i.e. higher CD4 counts) and risk of MCD[125,126]. According to the notion that KS development is rather more dependent on HHV8-specific immune failure than MCD, 12 MCD cases were demonstrated to be constantly associated with polyfunctional effector memory $CD8^+$ cells ($EMCD8^+$) in PBMC, showing, in particular, high magnitudes of HHV8-specific advanced differentiation stage T-cell repertoires (i.e. the expansion of virus-specific $CCR7^-$ $CD27^-$ $CD45RA^-$ late $EMCD8^+$), which, in turn, may be in strict relation to the high viral loads[127]. On the contrary, the peer EBV-specific $EMCD8^+$ are frequently absent in patients with EBV-associated AIDS-related non-Hodgkin's lymphoma. By comparison, 12 asymptomatic HIV-positive control subjects with low levels of HHV8-positive replication mainly showed $CCR7^-$ $CD27^+$ $CD45RA^-$ early/intermediate $EMCD8^+$, which are known to be associated with the effective immune control of viral infections[127,128]. In summary, a consistent model of $CD8^+$ memory T-cell responses against HHV8 has been proposed for different clinical situations, namely the asymptomatic HHV8 carrier state, mainly displaying an early/intermediate $EMCD8^+$ profile, the KS disease associated with absence of EM, and the MCD associated with late

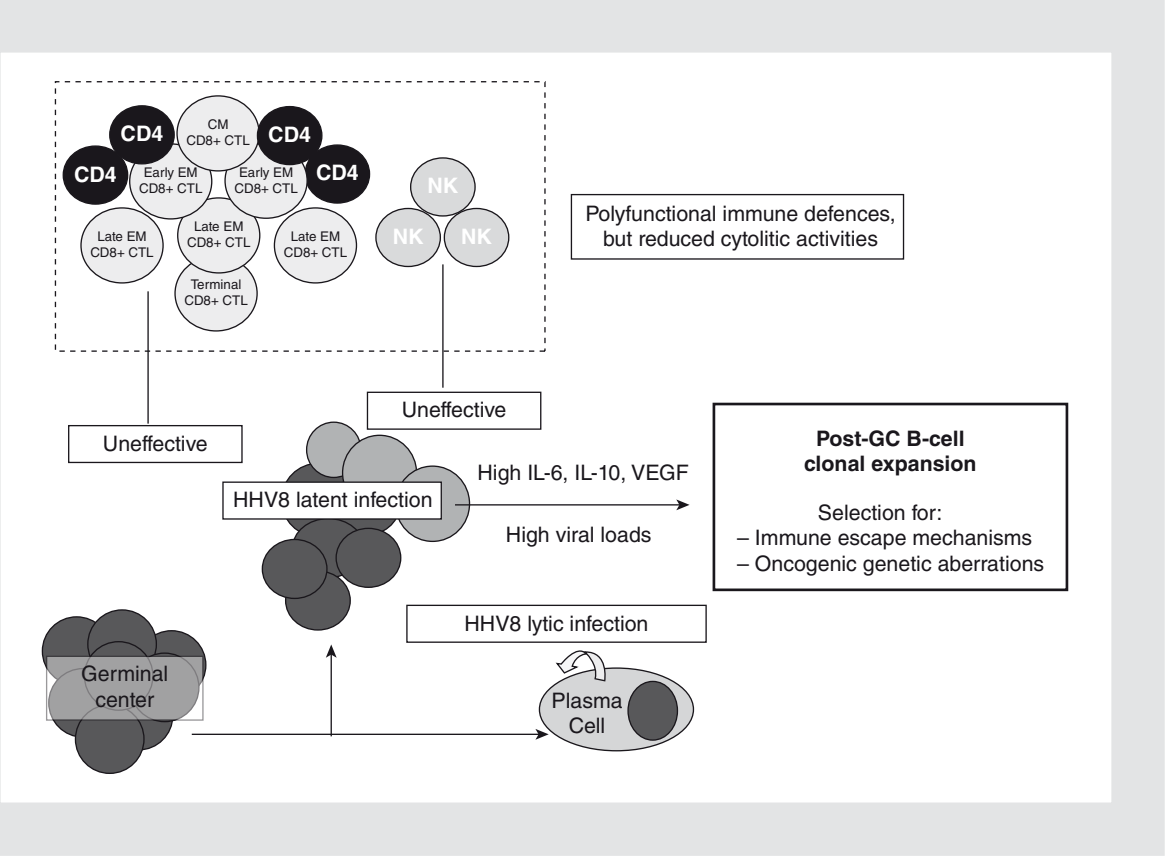


**Figure 3.** *Immune-inflammatory environment allowing the expansion of HHV8-associated lymphoproliferative diseases. NK: natural killer; EM: effector memory; CTL: cytotoxic T lymphocyte; HHV8: human herpesvirus 8; IL: interleukin; VEGF: vascular endothelial growth factor; GC: germinal center.*

EMCD8$^+$ expansion[127]. Nonetheless, by confirming that a determinant level of immune escape should also be reached to allow for HHV8-positive lymphoma progression, fully differentiated (CD45RA$^+$) EMCD8$^+$ showed similarly low magnitudes both in MCD as in asymptomatic HHV8-positive patients[127]. In addition, we could also detect HHV8-specific IFNγ responses in PBMC from three out of four MCD or PEL HIV-negative patients (unpublished data), further supporting the notion that both types of HHV8-positive lymphoproliferation may be associated with detectable (but ineffective) immune responses, which are failing to eradicate the viral antigen burden, thus becoming permissive to related disease onset.

Rituximab treatment has been reported to be clinically useful both to reduce HHV8 viral loads and to control the related diseases, as with EBV-associated lymphomas[129-131]. However, immunological investigations should now address the emerging issue of KS flare in MCD patients treated with rituximab, since anti-CD20 immunotherapy may affect important cross-talks among adaptive and innate immune compartments[132,133]. Finally, based on the outstanding results provided by antiviral treatments against HCV-associated B-cell lymphomas, and the detection of fine correlations between HHV8 DNA viremia and the evolution of HHV8-positive lymphoproliferative diseases, further studies are required to improve the therapeutic potential of antiviral agents, such as ganciclovir or intracavitary cidofovir, against MCD and PEL, respectively[134-138].

## Conclusions and clinical perspectives

As reviewed in this paper, the relevance of immune recovery in the control of KS disease after reduction of immunosuppressive therapy should encourage multifunctional T-cell monitoring and adoptive T-cell immunotherapeutic protocols, already presented as valuable strategies against other pathogen-associated diseases[13,81-84,139,140]. However, the specific active contribution of immune-inflammatory dysregulation to the early onset of KS supports the rational use of different classes of immunomodulatory drugs (such as mTOR inhibitors, IL-12), as a new chance to deeply impact

on KS pathology and improve the outcome of affected immunocompromised patients. In a clinical perspective, immunological monitoring of changes in HHV8-specific T-cell responses in the KS setting could be directly useful to support the clinical decision-making process during the follow-up of HIV-positive and post-transplant patients. In the management of HHV8-positive lymphoproliferative diseases, even more detailed immunological markers of disease activity are required to track clinically relevant immune dynamics and, concurrently, test the clinical efficacy of innovative antiviral treatments[47,128,141-143].

## Acknowledgements

This study was supported by the the Associazione Italiana per la Ricerca sul Cancro (AIRC), Milan, Italy; the European Commission's FP6 Life-Science-Health Programme (INCA project; LSHC-CT-2005-018704); the Associazione Italiana Lotta alle Leucemie, Linfoma e Mieloma (AIL)-Modena-ONLUS; and the Programma di ricerca Regione-Università 2007-2009.

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