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# KSHV Paracrine Effects on Tumorigenesis

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## 1. Introduction

In 1994, Chang and colleagues isolated two viral DNA fragments from Kaposi's sarcoma (KS) patients which showed homologies to, but were distinct from, genes coding for capsid and tegument proteins of two herpesviruses - namely, Epstein-Barr virus and Herpesvirus saimiri (Y. Chang et al., 1994). These new herpesvirus-like sequences led to the definition of a new human herpesvirus, namely, Kaposi's sarcoma-associated herpesvirus (KSHV, or human herpesvirus type-8, HHV-8). Shortly afterwards it was shown that KSHV is closely associated with KS tumours (Dupin et al., 1995; Huang et al., 1995; Moore & Chang, 1995), indicating that KSHV is the etiologic agent of KS.

KSHV infection can be detected in several different cell types, including B-cells (Monini et al., 1999), T-cells (Harrington et al., 1996; Sirianni et al., 1997b), monocytes (Blasig et al., 1997), macrophages (Sirianni et al., 1997a), endothelial cells (Boshoff et al., 1995), and dendritic cells (Rettig et al., 1997). Apart from KS, infection with KSHV leads to the development of two other tumour diseases: primary effusion lymphoma (PEL), and a subset of multicentric Castleman's disease (MCD) (Cesarman et al., 1995; Soulier et al., 1995). While PEL and MCD are primary disorders of the B-cell lineage, KS originates from endothelium-derived cells. KS is classified into four different epidemiological forms: classic KS, iatrogenic KS, African endemic KS, and AIDS-associated epidemic KS. All forms have the same histological features, but reveal different progression rates and risk factors, and evolve in different populations (Friedman-Kien & Saltzman, 1990).

The classic KS primarily affects elderly men of Eastern European or Mediterranean origin and usually proceeds very slowly. Patients receiving immunosuppressive therapy (e.g. after solid-organ transplantation) are at increased risk for iatrogenic KS. This rare form of KS is more aggressive than classic KS (Stickler & Friedman-Kien, 1991). The interruption or modulation of the immunosuppressive therapy is usually sufficient for the regression of iatrogenic KS (Stallone et al., 2005; Wijnveen et al., 1987). The African endemic KS is much more aggressive and affects adults as well as children, predominantly in Sub-Saharan Africa (Stickler & Friedman-Kien, 1991). In the endemic regions, KS accounts for up to 13% of all malignancies (Parkin et al., 2008). The most clinically aggressive form of KS is the AIDS-associated epidemic KS (AKS). This entity is the most common cancer in

patients infected with the human immunodeficiency virus type-1 (HIV-1). HIV-1-positive homosexual men are predominantly affected (J.N. Martin et al., 1998). The fact that co-infection with HIV-1 acts as co-factor for AKS development is specifically supported by the significant decline of AKS incidence after the introduction of highly active anti-retroviral therapy (HAART) for treatment of HIV-1 infection (J. Gill et al., 2002; Ledergerber et al., 1999). Nevertheless, KS is still among the most commonly observed tumours in certain regions of central Africa, and is a clinical threat for organ transplant recipients (Parkin et al., 2008; Trattner et al., 1993).

In 1996, the complete genome sequence of KSHV was made available, indicating that KSHV encodes more than 86 genes (Neipel et al., 1997; Russo et al., 1996). The large KSHV genome provides innumerable possibilities to interfere with cellular signalling cascades in the course of the viral life cycle and thereby induce tumorigenesis. It is still an unsolved question how KSHV may initiate and/or perpetuate KS development. Research on KS tumorigenesis was hampered for long time by the fact that an efficient *in vitro* culture system for KSHV infection and replication in endothelial derived cells was lacking. Moreover, an appropriate animal model system in which KSHV transmission causes KS is missing. Sporadic observations of KS development in common marmosets (New World primates) require still further confirmation (H. Chang et al., 2009). In this chapter, we will review the histopathology of KS and the oncogenic potential of KSHV.

## 2. KS histogenesis and the biology of the KS spindle cells

KS was first described by Moritz Kaposi in 1872 as an idiopathic multiple pigment sarcoma of the skin (Kaposi, 1872). KS is a multifocal, highly vascularised tumour of endothelial origin with a complex histology. Apart from KSHV-positivity, KS lesions contain three further hallmarks — (1) a pronounced inflammatory infiltrate composed of monocytes, macrophages, T-cells and dendritic cells, (2) neovascular spaces, which are incomplete or dilated vessel-like structures, often associated with extravasated erythrocytes and oedema, and (3) predominantly in later stages of tumour development, bundles of spindle shaped cells, which are called the KS spindle cells and are considered to be the tumour cells of KS (Gottlieb & Ackerman, 1988; Grayson & Pantanowitz, 2008; Stickler & Friedman-Kien, 1991). The tumour occurs at onset predominantly in the skin, visceral organs, and lymph nodes, while in progressed late stages, all organs can be affected (Pantanowitz & Dezube, 2008). KS evolves over time from the early patch stage to the intermediate plaque stage and manifests later on into a nodular stage. The patch stage is characterized by pinpoint macules on the skin with proliferating endothelial cells, which form the slit-like neovascular structures. These neovascular channels are only partially lined with KSHV-positive cells (Dupin et al., 1999), lack coating by pericytes or smooth muscle cells, and are prone to leakage and rupture (McNutt et al., 1983). Early-stage lesions are further characterized by the presence of infiltrating inflammatory cells such as macrophages, monocytes, dendritic cells, and B- and T-cells (Gottlieb & Ackerman, 1988). Productive KSHV infection of B-cells, monocytes, and macrophages within KS lesions has been described (Ascherl et al., 1999a; Blasig et al., 1997; Stürzl et al., 2001), indicating that these cells may represent the viral replication reservoirs. In the plaque stage, flat macules and patches start to enlarge vertically to slightly elevated lesions termed papules or plaques. In this stage, the typical KS spindle cells appear. In the nodular stage, the KS spindle cells become the predominant cell type. Up to 80% of these cells are infected by KSHV, wherein the virus resides mainly in the latent stage of the viral

life cycle (Staskus et al., 1997; Stürzl et al., 1997). These cells were initially considered as the main proliferating element of KS.

The nature of the KS spindle cells has been debated for many years. Nowadays, it is commonly accepted that the spindle cells are of endothelial origin, as most of them express markers of both lymphatic and blood vessel derived endothelial cells (Boshoff et al., 1995; Stürzl et al., 1992a). However, whether these cells originate from lymph or blood vessel endothelial cells (LECs and BECs respectively) is still not unequivocally proven. Initial *in vivo* studies of AIDS- and classic KS showed that the KS spindle cells are of endothelial origin (CD31-positive), and related to, or even derived from, LECs. The KS spindle cells stained positive for the typical lymph endothelial markers vascular endothelial growth factor receptor (VEGFR)-3 and podoplanin (Dupin et al., 1999; Skobe et al., 1999; Weninger et al., 1999), but were negative for BEC marker (Beckstead et al., 1985; Roth et al., 1992), excluding their origin from blood vessel or hematopoietic cells.

However, several further studies showed that KSHV does not only infect LECs, but also BECs (Carroll et al., 2004; Moses et al., 1999; Poole et al., 2002). Microarray analyses revealed that infection with KSHV seems to induce a cellular reprogramming of each cell type towards the gene expression profile of the other, driving these cells away from their terminally differentiated state towards the opposing lineage (Hong et al., 2004; Petrova et al., 2002; H.W. Wang et al., 2004). This was supported by observations that KSHV-infection of BECs led to increased expression of LEC markers such as VEGFR-3, podoplanin, LYVE-1, PROX1, VEGF-A and VEGF-C (Carroll et al., 2004; Sivakumar et al., 2008), while in parallel, KSHV infection of LECs led to increased expression of BEC markers (H.W. Wang et al., 2004). Thus, the resulting infected LECs or BECs are more similar to one another than their uninfected counterparts. This is in agreement with the observation that KS spindle cells do not represent the typical transcriptional profile of LECs nor of BECs, but instead are poorly differentiated, expressing markers of both lymphatic and blood vessel endothelium (Cornelissen et al., 2003; Lagos et al., 2007; Pyakurel et al., 2006b; H.W. Wang et al., 2004).

Currently, two hypotheses describe the origin of the KS spindle cells: the first hypothesis suggests that KSHV infects both BECs and LECs, and induces a transcriptional dedifferentiation towards the gene expression profile of an endothelial precursor cell (EPC) (R. Liu et al., 2010). This hypothesis is supported by the studies of Chang et al., where a high-throughput approach was employed to study the genome-wide alternative splicing events in LECs and $CD34^+$ EPCs (T.Y. Chang et al., 2011). The authors found a significant difference in the exon usage between LECs and $CD34^+$ EPCs, and observed that KSHV infection of LECs resulted in a LEC-to-precursor dedifferentiation-like reprogramming. Moreover, it seems that KSHV prefers LECs, as (1) mature endothelial cells surrounding normal vascular blood vessels within a KS lesion are only very rarely infected with KSHV (Dupin et al., 1999; Lorenz, 2007) and (2) LECs exhibit an increased number of viral genome copies per cell compared to BECs, indicating that the virus replicates more efficiently in LECs than in BECs (H.W. Wang et al., 2004). The second hypothesis suggests that KSHV productively infects and replicates in $CD34^+$ EPCs, which might serve as the KSHV reservoir (Della Bella et al., 2008; Henry et al., 1999; Pellet et al., 2006; Wu et al., 2006). This is in accordance with the observation that $CD34^+$ circulating endothelial cells are increased in classic KS patients (Taddeo et al., 2008) and that KSHV-infected $CD34^+$ hematopoietic progenitor cells are transmitted through the graft during transplantation (Barozzi et al., 2003). KSHV infection of circulating EPCs might drive their gene expression profile towards a more lymphatic genotype. This would explain the simultaneous expression of marker proteins for lymphatic endothelial cells, blood vessel endothelial cells, and pericytes, which originate all from $CD34^+$ EPCs.

## 3. KS tumorigenesis

As detailed above, KS lesions display a remarkable diversity of cell types, dominated by endothelial-derived KS spindle cells (Regezi et al., 1993; Stürzl et al., 1992a). While the infiltrating inflammatory cells appear already during the early patch stage, the KS spindle cells start to appear in the intermediate plaque stage and are present in increased numbers in late nodular stages. In the late stages of KS, nearly all spindle cells are infected (Dupin et al., 1999; Katano et al., 2000; Staskus et al., 1997; Stürzl et al., 1997), indicating that the spindle cells constitute the main tumour mass of KS. The abundance of spindle cells in late stage lesions is thought to derive from the growth and/or survival advantages of infected over uninfected cells due to oncoviral transformation by KSHV.

### 3.1 KS: Reactive hyperplasia rather than true malignancy?

Among the oncoviruses, especially throughout the herpesviruses, virus-induced transformation of cells occurs mostly due to the continuous expression of viral proteins in the host cell. For example, among the closest relatives of KSHV, the herpesvirus saimiri (HVS) transforms T-cells by expressing the saimiri transformation-associated protein (Stp) and in the HVS subgroup C additionally the tyrosine kinase-interacting protein (Tip) (Biesinger et al., 1995; Duboise et al., 1998; Murthy et al., 1989), while the Epstein-Barr virus (the only other known member of the human pathogenic gamma-herpesviruses) transforms resting primary human B-cells by continuously expressing the latent membrane protein-1 (LMP-1) (D. Wang et al., 1985). In contrast, it is still unclear whether KSHV-infection results in full tumorigenic cell transformation, and the underlying mechanisms of KS tumorigenesis are unknown. Several studies have tried to address these questions, but the mechanisms of cell alteration used by KSHV differ from that of other oncogenic viruses.

One crucial question is whether KS represents a hyperplastic proliferation or a clonal neoplastic growth. Several features indicate a neoplastic transformation of the KS spindle cells, such as anchorage independent growth and prolonged survival due to increased telomerase activity (Chen et al., 2001; Flore et al., 1998; Moses et al., 1999), protection from apoptosis (Mori et al., 1996; Morris et al., 1996; Stürzl et al., 1999; Thurau et al., 2009), increased angiogenesis, inflammation, invasion and metastasis (Gottlieb & Ackerman, 1988), genomic instability (Cuomo et al., 2008; Pan et al., 2004; Pyakurel et al., 2006a; Si & Robertson, 2006), and immune evasion strategies (Means et al., 2002), as well as the ability to reprogram the cellular metabolism (Karki et al., 2011; Montaner, 2007). Moreover, two studies indicated monoclonal expansion of KS. In the first study, KS clonality has been assessed by determining the methylation pattern of the X-linked androgen receptor gene (HUMARA) (Rabkin et al., 1997). The authors proved concordance among the methylation pattern of the HUMARA alleles in several different KS tumours from a given patient (in total, 8 female patients), indicating that multiple KS lesions in the same patient arise from a single clone of cells (Rabkin et al., 1997). The second study examined the clonal loss of the Y-chromosome in 20 of 23 male KS biopsies, as analysed by comparative genomic hybridisation (CGH) analysis (Pyakurel et al., 2006a). However, this study did not clarify if KSHV preferentially infects endothelial precursor cells that have sporadically lost their Y-chromosome or whether KSHV infection triggers the loss of the Y chromosome.

In contrast, a considerable amount of evidence is supporting a hyperplastic process of tumour development. First, KS spindle cells seem to be incompletely immortalised. This is indicated by the fact that (1) explanted KS cells are strongly dependent on external cytokines

and growth factors for the growth *in vitro* (Ensoli et al., 1989; Roth et al., 1989) and for the induction of tumours in immunodeficient mice (Salahuddin et al., 1988) and (2) KS spindle cells loose their ability to proliferate *ad infinitum* after explantation (Gao et al., 2003; Grossmann et al., 2006; Roth et al., 1989).

Second, KSHV-infected spindle cells do not exhibit enhanced proliferation in KS lesions, but on the contrary, show significantly reduced proliferation rates as compared to uninfected cells (Kaaya et al., 2000; Kaaya et al., 1995; Köster et al., 1996). In this context, Pyakurel and colleagues showed that only a small fraction (up to 5%) of all latency-associated nuclear antigen (LANA)-1-positive KS spindle cells proliferate in KS lesions (Pyakurel et al., 2004). Our data confirmed these findings (Lorenz, 2007). KS lesions were stained for LANA-1 as a marker for infected cells (Fig. 1C, brown staining) and for Ki67 as a marker for proliferating cells (Fig. 1C, blue staining). Using double staining procedure of KS lesions, we could demonstrate that KSHV-infected cells were only rarely proliferating, while the main proliferating population was composed of uninfected cells (Fig. 1C). By contrast, in body cavity based lymphoma cells, most of the infected cells (Fig. 1A, LANA-1, brown staining) are also proliferating (Fig. 1B, Ki67, brown staining). Thus, in KS lesions, the KSHV-infected cells do not represent the major proliferative element.

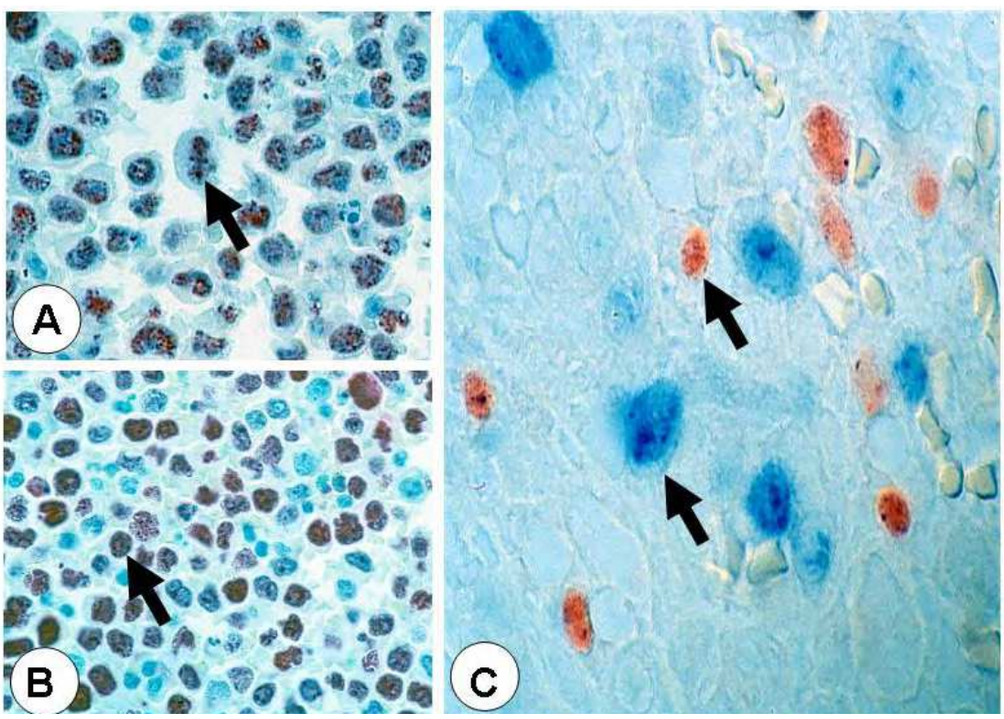


Fig. 1. KSHV infection and cell proliferation in body cavity-based lymphomas (A, B) and KS (C). Immunohistochemical detection of KSHV-LANA-1 (A) and of the proliferation-associated antigen Ki67 (B) in body cavity-based lymphoma cells shows that almost every infected cell is proliferating. Immunohistochemical double staining procedure of KSHV-LANA-1 (C, brown staining) and of the proliferation-associated antigen Ki67 (C, blue staining) in KS tissue shows that KSHV-infected cells are only rarely proliferating and that the major proliferative activity is observed in non-infected cells. Examples of positively stained cells are indicated by arrows.

Third, several studies provided evidence that KS expansion is polyclonal. The largest study was performed in 2007 on 62 biopsies. In order to investigate the cellular clonality of KS lesions, the authors determined the size heterogeneity of the KSHV-fused terminal repeat region (Duprez et al., 2007). The authors revealed in 59 cases a clonal pattern. Of those, 11 KS lesions were monoclonal, while 48 were oligoclonal expansions. Other studies sustain these findings, although performed with a smaller number of biopsies (Delabesse et al., 1997; P.S. Gill et al., 1998; Judde et al., 2000).

Fourth, KS lesions show a substantial rate of spontaneous remission, observed after the introduction of HAART (J. Gill et al., 2002; Ledergerber et al., 1999), cessation of immunosuppression (Kondo et al., 2000; Nagy et al., 2000), or treatment with ganciclovir or foscarnet, which selectively inhibits lytic KSHV replication (Glesby et al., 1996; Mocroft et al., 1996). Together, these features imply that KS is not a true malignancy, but rather a polyclonal reactive hyperplasia.

### 3.2 Contribution of latency and lytic replication to KS tumorigenesis

As typical for herpesviruses, KSHV establishes a latent state of infection after entering the cell. During latency, only a few viral genes are expressed, among them are the LANA-1, viral cyclin, viral FLICE-inhibitory protein (vFLIP), Kaposin, and the viral-encoded microRNAs. All of the latently expressed proteins have been shown to have individual transforming potential by driving cell proliferation and preventing apoptosis (Friborg et al., 1999; Muralidhar et al., 1998; Radkov et al., 2000; Stürzl et al., 1999; Stürzl et al., 2001; Sun et al., 2003; Verschuren et al., 2002). Therefore, it was long assumed that latently expressed proteins are involved in KS tumorigenesis and that latently infected cells contribute significantly to the development of KS. The fact that most of the KS spindle cells are latently infected is in line with the herpesviral persuasion that the latency program drives tumorigenesis.

Nevertheless, several lines of evidence suggest that latent replication is not sufficient to induce KS. First, KS is typically observed in patients with higher circulating KSHV loads, indicating that lytic expression is necessary for the recruitment and *de novo* infection of cells (Campbell et al., 2000; Whitby et al., 1995). Second, ganciclovir and foscarnet have been shown to mediate the long-term remission of KS (Glesby et al., 1996; Mocroft et al., 1996), again indicating that ongoing lytic replication is necessary for lesion formation. Third, immunosuppression favours KS development, and this is connected with KSHV reactivation and lytic replication (Bourboulia et al., 2004; D.F. Martin et al., 1999). Fourth, cells expressing only latent genes are unable to induce tumour formation in nude mice, unless cells expressing viral G protein-coupled receptor (vGPCR), a lytic cycle protein, are co-injected (Montaner et al., 2006). A contribution of lytic replication to the development of KS is further sustained by the fact that a minority of cells within KS lesions do express lytic viral proteins and produce virions (Orenstein et al., 1997; Staskus et al., 1997).

By now, the crucial question arises concerning the way lytically infected cells might contribute to KS tumour development, albeit (1) only up to 2% of the infected cells within KS lesions replicate lytically and (2) all lytically infected cells die after virus release. The common hypothesis is based on the fact that KSHV encodes many viral lytic genes whose products are secreted factors homologous to cellular chemokines, cytokines, and growth factors, such as the viral interleukin (IL)-6 and the three viral chemokines (vCCL-1, -2, and -3, or alternatively named viral macrophage inflammatory protein, vMIP-I, -II, and III)

(Nicholas, 2003). The vIL-6 is produced and released by infected cells during lytic infection and activates cell proliferation (Meads & Medveczky, 2004) and local angiogenesis (Aoki et al., 1999), while the viral MIPs are agonists for cellular chemokine receptors and exhibit angiogenic properties (Boshoff et al., 1997; Endres et al., 1999; C. Liu et al., 2001; Stine et al., 2000). The vMIP-I was shown to induce the migration of endothelial cells, which suggests that uninfected endothelial cells are recruited to the KS lesion as a target for infection (Haque et al., 2001) and vMIP-II was demonstrated to be a selective chemoattractant for Th2 cells and monocytes (Sozzani et al., 1998). Furthermore, two KSHV transmembrane proteins – K1, an immunoreceptor tyrosine-based activation motif (ITAM) containing receptor, and vOX2, a glycosylated cell surface protein belonging to the immunoglobulin superfamily homologous to the cellular OX2 protein – are suggested to be important for secretion of cellular inflammatory cytokines and growth factors. K1 induces the expression of VEGF and matrix metalloproteinase-9 (MMP-9) in endothelial cells (L. Wang et al., 2004), indicating its role in proliferation and migration of these cells. Solubilised vOX2 stimulates monocytes, macrophages, and dendritic cells to produce the inflammatory cytokines IL-1β, IL-6, monocyte chemoattractant protein 1 (MCP-1), and tumour necrosis factor α (TNF-α) (Chung et al., 2002). Thus, lytically infected cells are thought to produce or activate signalling molecules which promote inflammation and angiogenesis in the KS lesions in a paracrine manner.

In addition, KSHV encodes a vGPCR, a homologue of the cellular IL-8 receptor CXCR2, which has a mutation within the highly conserved DRY sequence, rendering the receptor constitutively active. Therefore, the vGPCR was long thought to play a key role in the initiation of KS. This was further enforced in 2003, when Montaner and colleagues succeeded in engineering a novel transgenic mouse that allowed endothelial cell-specific retroviral transduction. With that technique, they expressed several single KSHV genes that were assumed to have oncogenic properties in mouse endothelial cells. The authors showed that the vGPCR was the only gene that was able and sufficient to induce angioproliferative tumours that resembled human KS (Montaner et al., 2003). Thus, lytically expressed vGPCR may contribute to KS pathogenesis. As vGPCR is a protein produced only during the lytic replication of KSHV, its expression should correlate with the rate of lytically replicating cells in KS lesions. Concordantly, in all KS mouse models, expression of vGPCR is restricted to a small subset of cells within the lesions, which is similar to the part of lytically replicating cells in human KS. This supports the hypothesis that vGPCR influences tumour growth by paracrine mechanisms promoted by the cytokines, chemokines, and growth factors secreted by vGPCR-expressing cells (Jham & Montaner, 2010). However, it remains to be proven if the vGPCR alone (together with latently infected cells) is sufficient to trigger KS tumorigenesis or additional factors are necessary.

### 3.3 Interplay between inflammatory cytokines and angiogenic factors in KS tumorigenesis

KS tumorigenesis is characterized by the interplay between three processes: proliferation, inflammation and angiogenesis. These processes are connected by paracrine signalling pathways driven by the interplay between viral gene products, inflammatory cytokines, and growth factors released not only by infected cells, but also by chemoattracted infiltrating inflammatory cells. KSHV-infected cells secrete factors, such as MCP-1 or granulocyte-macrophage-colony-stimulating factor (GM-CSF), to recruit and activate inflammatory cells

(especially $CD8^+$-T-cells, plasma cells, monocytes and macrophages) to the site of infection (Barillari et al., 1992; Ensoli & Stürzl, 1998; Sciacca et al., 1994). To further enhance the infiltration and binding of immune cells within the lesions, KS spindle cells express additionally high levels of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin (Fiorelli et al., 1995; Galea et al., 1998). The recruited and activated infiltrating inflammatory cells in turn release inflammatory cytokines (IC), such as IFN-γ, IL-1β, TNF-α, and IL-6, which are essential for the activation and proliferation of cells comprised in the KS lesions. Interestingly, these cytokines can induce uninfected endothelial cells to acquire the phenotypic and functional features of KS spindle cells (Fiorelli et al., 1998; Monini et al., 1999; Qin et al., 2010; Samaniego et al., 1995; Sirianni et al., 1998; Stürzl et al., 1995). In accordance, these cytokines are also detected *in vivo* at increased concentrations in the serum of patients with all forms of KS and of individuals at high risk for KS (Emilie et al., 1990; Ensoli et al., 1992; Fuchs et al., 1989; Hober et al., 1989).

The presence of an inflammatory milieu is further supported by several studies that have been performed to analyse the impact of KSHV infection on the transcriptome or proteome of endothelial cells. KSHV-infection is associated with a strong IFN-related cell response. Up-regulation of several interferon-inducible proteins, interferon-induced transmembrane protein 1 (IFI9-27), myxovirus resistance protein 1 (MxA), CXCL11, and members of the guanylate binding protein (GBP) family were observed (Chandriani & Ganem, 2007; Lagos et al., 2007; Moses et al., 2002; Naranatt et al., 2004; Poole et al., 2002; Stürzl et al., 2009). Of these factors, especially GBP-1 has been shown to have antiangiogenic effects in endothelial cells *in vitro* and *in vivo* (Guenzi et al., 2001; Guenzi et al., 2003; Hammon et al., 2011; Lubeseder-Martellato et al., 2002; Naschberger et al., 2008), which might explain the observed reduced proliferation rate in infected spindle cells within KS lesions.

Additionally to the IC, the infiltrating inflammatory cells release the angiogenic growth factors basic fibroblast growth factor (bFGF) and VEGF, which are known to induce angiogenesis, vascular permeability, and oedema, the typical histological features of KS (Barillari et al., 1992; Barillari et al., 1999; Samaniego et al., 1998). These angiogenic growth factors were detected at increased concentrations in the serum of HIV-1 infected patients, supporting their important role in KS pathogenesis (Ascherl et al., 1999b). Furthermore, another growth factor, namely PDGF-B, was shown to be an important paracrine mitogen in KS lesions. *In vitro*, PDGF-B activates the proliferation and migration of KS spindle cells. *In vivo* gene expression analysis revealed that PDGF-B, as well as the PDGF-receptor, is present in KS lesions (Köster et al., 1996; Stürzl et al., 1995; Stürzl et al., 1992b). Accordingly, treatment of AIDS-related KS patients with imatinib, an inhibitor of the PDGF-receptor, induced clinical regression of KS in five out of ten patients within four weeks of therapy. Imatinib is also active against c-kit, another receptor tyrosine kinase that has been implicated in KS formation. Thus, further molecular studies and clinical trials are necessary to better elucidate the significance of PDGF-receptor and c-kit expression in KS and the therapeutic role of imatinib (Koon et al., 2005; Rossi et al., 2009).

The angiogenic environment in the KS lesions is further promoted by numerous paracrine or juxtacrine active proteins expressed by KSHV-infected cells. For example, increased expression of Angiopoeitin-2 (Ang-2), angiopoietin-related protein 4, angiopoietin-like polypeptide, ephrins A1 and B2, endothelin convertase, serpin B2 (plasminogen activator inhibitor 2), VEGF-A and -C, thrombomodulin, members of the matrix metalloproteinases

(MMP-1 and -9), urokinase-type plasminogen activator receptor, CXCR7, and MCP-1 has been observed upon KSHV infection (Chandriani & Ganem, 2007; Cornali et al., 1996; Moses et al., 2002; Naranatt et al., 2004; Poole et al., 2002; Thewes et al., 2000; Vart et al., 2007). Of those, Ang-2 is thought to destabilise endothelial cells interaction and to prime endothelial cells to respond to angiogenic stimuli, such as VEGF (Gale et al., 2002). It also plays an important function in lymphangiogenesis (Gale et al., 2002) and regulates the expression of inflammatory proteins in endothelial cells (Fiedler et al., 2006).

Moreover, lytically replicating KSHV-infected cells express a vGPCR, which has the ability to up-regulate the activity of numerous transcription factors, such as hypoxia inducible factor-1α (HIF-1α), nuclear factor-kappaB (NF-κB), activator protein-1 (AP-1), cAMP response element-binding protein (CREB) and nuclear factor of activated T cells (NFAT), and thereby mediates the secretion of paracrine factors promoting endothelial cell survival, proliferation and angiogenesis. Among the paracrine-acting factors are angiogenic growth factors such as VEGF, bFGF, and VEGFR-2, pro-inflammatory chemokines and cytokines such as IL-1β, IL-2, IL-4, IL-6, IL-8, MIP-1, and TNF-α, and adhesion molecules such as ICAM-1, VCAM-1, and E-selectin (Arvanitakis et al., 1997; Bais et al., 1998; Grisotto et al., 2006; D. Martin et al., 2008; Montaner et al., 2004; Schwarz & Murphy, 2001; Sodhi et al., 2000; Yang et al., 2000).

In summary, viral proteins and virus-induced cellular proteins are secreted by infected cells and act in autocrine and paracrine loops to recruit inflammatory cells into the lesions, which in turn secrete inflammatory cytokines, chemokines, and angiogenic growth factors. The fact that KSHV-infection leads to up-regulation of angiogenesis-related and interferon-inducible genes in endothelial cells highlights the importance of an inflammatory-angiogenic milieu during KS tumorigenesis. This is further sustained by the observation that these genes are strongly transcribed, although KSHV encodes a DNA exonuclease SOX/orf37, which mediates the shut-off of host transcription during the lytic cycle of KSHV (Chandriani & Ganem, 2007). All these secreted proteins appear to cooperate in the activation of endothelial cells and are important for tumour neovascularisation and KS development (Ensoli et al., 1992; Ensoli et al., 1989; Ganem, 1995; Safai et al., 1985).

### 3.4 Paracrine model of KS tumorigenesis

The presence of paracrine-acting factors in KS lesions and the transcriptome analyses of infected endothelial cells (see above) argue for a paracrine stimulation of proliferation in the KS lesions. The current theory is that the paracrine-driven cell proliferation is promoted by the concerted action of latent and lytic gene products inducing a specific "tumorigenic" environment of growth factors and cytokines. In this scenario, KSHV-infected cells may stimulate the proliferation of uninfected endothelial cells in the vicinity and/or recruit endothelial cells in a paracrine manner, and thereby increase the number of target cells for *de novo* infection with virus particles released from lytic replicating cells. Accordingly, proliferation might be driven by latently, and a few lytically, infected cells, and the initial tumour mass might be predominantly formed by uninfected endothelial cells (in early lesions). The abnormal cell proliferation of uninfected endothelial cells may contribute to the increased formation of dilated vessels with abnormal structure and the formation of spindle cells observed in the course of KS development. Subsequent KSHV infection of these cells may predominantly result in a survival advantage of these cells with reduced proliferation rate, overall resulting in the stabilisation of KS lesions. This is supported by several data.

First, KS spindle cells exhibit up-regulation of the VEGFR and increased response to growth factors (Brown et al., 1996; Flore et al., 1998; Sivakumar et al., 2008). Second, KS spindle cells show increased protection against apoptosis, mainly through activation of the NF-κB signal transduction pathway (Keller et al., 2000; Konrad et al., 2009; Stürzl et al., 1999; Thurau et al., 2009). Third, in KS spindle cells, the prosurvival phosphatidylinositol 3-kinase/Akt signal transduction pathway is activated (Montaner et al., 2001; L. Wang & Damania, 2008). Finally, infection of endothelial cells with KSHV increases telomerase activity (Flore et al., 1998), causing prolonged growth and survival of the infected cells beyond their natural lifespan. Thus, during the progression of KS, more and more endothelial cells might be attracted to the lesions and become infected with KSHV, thereby resulting in the histological presentation observed above (Fig. 1): a high number of latently infected spindle cells with a low proliferation rate.

## 4. Acknowledgements

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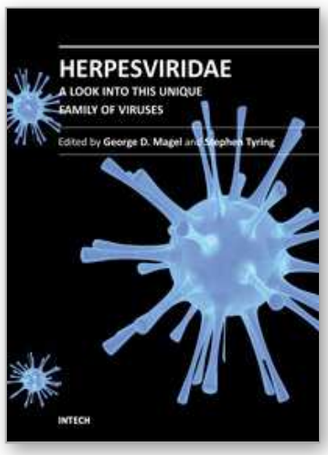


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In order to fully understand the nature of viruses, it is important to look at them from both, their basic science and clinical, standpoints. Our goal with this book was to dissect Herpesviridae into its biological properties and clinical significance in order to provide a logical, as well as practical, approach to understanding and treating the various conditions caused by this unique family of viruses. In addition to their up-to-date and extensive text, each chapter is laced with a variety of diagrams, tables, charts, and images, aimed at helping us achieve our goal. We hope that this book will serve as a reference tool for clinicians of various specialties worldwide.

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