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Kaposis sarcoma herpesvirus-induced endothelial cell reprogramming supports viral persistence and contributes to Kaposis sarcoma tumorigenesis

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Kaposis sarcoma (KS) is an endothelial tumor causally linked to Kaposis sarcoma herpesvirus (KSHV) infection. At early stages of KS, inflammation and aberrant neoangiogenesis are predominant, while at late stages the disease is characterized by the proliferation of KSHV-infected spindle cells (SC). Since KSHV infection modifies the endothelial cell (EC) identity, the origin of SCs remains elusive. Yet, pieces of evidence indicate the lymphatic origin. KSHV-infected ECs display increased proliferative, angiogenic and migratory capacities which account for KS oncogenesis. Here we propose a model in which KSHV reprograms the EC identity, induces DNA damage and establishes a dysregulated gene expression program involving interplay of latent and lytic genes allowing continuous reinfection of ECs attracted to the tumor by the secretion of virus-induced cellular factors.

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Kaposis sarcoma and identification of its associated herpesvirus

Kaposis sarcoma (KS) was named after a Hungarian dermatologist, Moritz Kaposi, who first described five cases of this multifocal, pigmented tumor of the skin. KS remained a rare disease until the 1980s when an aggressive form was observed among the AIDS patients. The high number of cases together with the bad prognosis associated with AIDS-KS prompted researchers on studying the disease in detail. Particular efforts were put into the identification of KS causal agent and in 1994 Chang and Moore identified it as a newly discovered virus named Kaposis sarcoma herpesvirus (KSHV) [1]. Classified as a gamma2 herpesvirus [2], KSHV has been subsequently associated also with two lymphoproliferative disorders: primary effusion lymphoma (PEL) and multicentric castleman disease (MCD) [3,4].

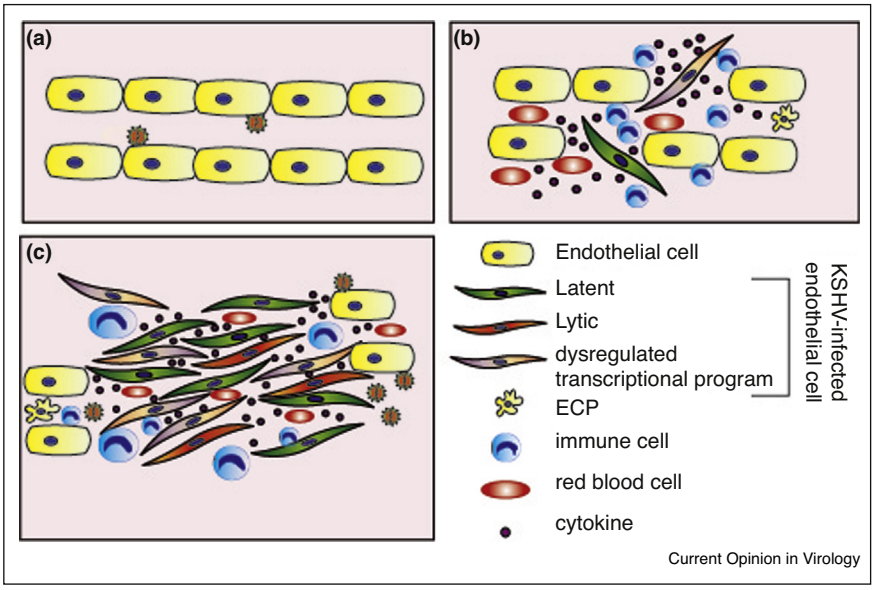
KSHV displays a biphasic life cycle with a latent and a lytic phase. Although latency represents the default mode of persistence in the tumor cells, both phases contribute to KS pathogenesis. Since many reviews [5–8] recently discussed the molecular mechanisms of KS induced tumorigenesis, here we will focus on the reprogramming and manipulation of endothelial cells and its contribution to KS pathogenesis.

KS: an angiogenic, inflammatory tumor of the endothelium

Different forms of KS can be distinguished according to their epidemiological characteristics. In the sub-Saharan Africa KS is a common tumor among men and children (epidemic KS), whereas in the Mediterranean basin a milder form of KS affects primarily elderly men (endemic KS) [9]. The clinical features of KS become more aggressive when it occurs in immunosuppressed patients, such as transplant recipients (iatrogenic KS) and AIDS patients (AIDS KS) [10,11]. In these individuals, the lesions are life threatening because of the visceral involvement [11].

Microscopically, the different forms of KS are indistinguishable and display rather stage-specific features. At the early phase, KS manifests as patches characterized by abundant and aberrant angiogenesis. The abnormal blood vessels are leaky, thus accounting for the extravasation of erythrocytes and inflammatory cells that populate the lesion (Figure 1). The early KS patch appears as a flat, red macula (located in the limbs or face) and no evident tumor mass is present. In these patches, as little as 10% of the tumor is composed of KSHV-infected cells. When progressing toward advanced stages, KS develops into plaques and then into nodules. Here, 90% of the cells are KSHV-positive. The tumor mass is macroscopically evident and composed of so-called spindle cells (SCs) [12] that is, KSHV-infected cells with characteristic, elongated (spindle) morphology (Figure 1).

Figure 1



Schematic model of a KS lesion **(a)** KSHV virions infect endothelial cells. **(b)** Early KS lesion: KSHV infected endothelial cells display the typical spindle morphology and produce pro-angiogenic and inflammatory cytokines that chemotactically attract immune cells to the tumor site. Aberrant angiogenesis takes also place and causes the extravasation and accumulation of red blood cells. **(c)** Late KS lesion: the tumor is composed of KSHV-infected SCs. Majority of the SC are in a latent/dysregulated lytic phase, produce inflammatory and angiogenic chemokines and express many oncogenic viral proteins. Only a small subset of SCs are in a lytic phase and they produce new infectious virions for the maintenance of the population of infected cells.

On the cellular origin of KS spindle cells

Different studies reported that SCs express a number of endothelial cell (EC) markers, for example, CD31, CD34 and factor VIII but they also harbor, to a lesser extent, lineage specific signatures of smooth muscle cells (α-SMA), monocytes/macrophages, dendritic cells as well as fibroblasts and mesenchymal cells [13,14••,15–18].

The gene expression signature of KS SCs indicates an endothelial origin; however, it is still a matter of debate whether the original precursor belongs to the blood or lymphatic lineage. KSHV infection of lymphatic ECs (LECs) triggers the reprogramming toward a less differentiated, immature blood ECs (BECs) phenotype, making KSHV-LECs more similar to BECs than their uninfected counterpart. KSHV-infected BECs, vice versa, express lower levels of blood vascular markers such as CXCR4 and Neuropilin-1 and show an increase in lymphatic markers like Prox1, VEGFR3, podoplanin and LYVE1 (reviewed in [19]). KSHV infection of ECs manipulates the EC differentiation program driving each cell type away from its original, mature phenotype and pushing it toward an undifferentiated, even mesenchymal-like cell type with mixed identity (reviewed in [20••]). As a result, KSHV-infected ECs display tumorigenic properties such as increased angiogenic, invasive and migratory abilities and, although not fully immortalized [21,22], they exhibit a growth advantage over their uninfected counterparts [14••,23].

Several observations suggest that LECs rather than BECs are the main precursor of SCs. First, the localization of KS lesions in tissues rich in lymphatics (e.g. skin and mucosa) [24–26]. Second, KSHV-LECs exhibit, in culture, the elongated (spindling) morphology, resembling KS-SCs, whereas in BECs the morphology is not significantly altered by KSHV infection. Third, LECs can be more efficiently infected and harbor a higher viral copy number [13]. In Addition, the comparison of the gene expression profile of nodular KS lesion with those of BECs and LECs showed that KS signature resembles, at least at this stage, more LECs than BECs [13]. Moreover, three-dimensional culture of KSHV-LEC as spheroids has been shown to recapitulate many of the features found in the KS lesions, among others the differential expression of endothelial and mesenchymal markers in virus-infected cells and the increased tumorigenic invasiveness in the 3D matrix [14••].

Still, the presence of KSHV-infected BECs in KS lesions cannot be ruled out. KSHV-BECs are found in the early KS patches, where virus-positive cells are lining the walls of aberrant blood vessels. However, in the advanced lesions, although representing the majority of the tumor