Chapter 9

KAPOSI’S SARCOMA AND THE LYMPHATICS

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Abstract: Kaposi’s sarcoma herpesvirus (KSHV) is the etiological agent of Kaposi’s sarcoma (KS). KS presents as multifocal, angiogenic lesions involving an inflammatory infiltrate and KSHV-infected spindle cells display characteristic markers of lymphatic endothelia. The precise origin of the spindle cell component of KS lesions is uncertain and may derive from the reprogramming of the transcriptome of endothelial cells or their precursors to adopt a lymphatic-like gene expression profile. The lymphotrophic nature of KSHV corresponds to its pathological association with two further AIDS-related malignancies: primary effusion lymphomas (PEL) and a plasmablastic variant of multicentric Castleman’s disease (MCD). KSHV infection of B-cells in lymph node follicles creates a reservoir for the persistence of KSHV infection that may influence the characteristics of the associated lymphomas.

Here we discuss the mechanisms of KSHV infection in the context of KS and KSHV-associated lymphomas and examine the potential for KSHV to determine the fate of cells associated with the lymphatic system.

Key words: Endothelial cells · KSHV · Kaposi’s sarcoma · Lymphangiogenesis · Spindle cells

Up to 20% of global incidents of cancer can be attributed to infectious agents, primarily viruses, which influence the genesis of malignancies through a variety of mechanisms. Papillomaviruses (HPV) of types 11, 16 and 32, the human herpesviruses Epstein-Barr virus (EBV) and Kaposi’s sarcoma herpesvirus (KSHV, or HHV8), polyomaviruses, hepatitis viruses B and C, human T-cell leukaemia virus-1 and the bacterium Helicobacter pylori are causally associated with a variety of malignancies (reviewed in [52, 59, 66]).
The majority of tumour-associated viruses establish a latent infection in the host cell following primary infection. This leads to the persistence of the viral genome in the host tissue with infected cells expressing a subset of viral genes. Transformation may result from direct disruption of cell growth and proliferation through dysregulation of host signalling pathways or the induction of growth factors (e.g. EBV and HPV). Alternatively, the infectious agent may not be inherently oncogenic and transformation is achieved through indirect mechanisms (e.g. Hepatitis B and C). Commensurate with the multi-factorial nature of cancer, additional factors may participate in establishing the transformed phenotype in infected cells. Such factors include host immunosuppression, carcinogetic exposure and genetic predisposition or additional somatic mutation. The presence or absence of the infectious agent may serve to define subsets of a given tumour or determine the progression of the disease (reviewed in [33, 52, 59]).

Kaposi’s sarcoma-associated herpesvirus (KSHV) is a γ2-herpesvirus (See Box 1) whose global seroprevalence varies from less than 1% in Japan, to over 50% in much of sub-Saharan Africa where KSHV infection is endemic [77]. KSHV has been recognised by the International Agency for Research Against Cancer (IARC) as a class I carcinogen [IARC, 1] and is considered the causative agent of Kaposi’s sarcoma (KS) according to the Hill criteria [70]. The global incidence of KS also correlates with the seroprevalence of KSHV in different countries (for review see [3]).

**Box 1–Biology of KSHV**

**Virus Evolution**

KSHV was discovered in 1994 following PCR-based Representational Difference Analysis, which identified unique DNA sequences in AIDS-KS that were absent in adjacent skin [18]. KSHV is a double-stranded DNA virus that belongs to the *Rhadinovirus* (γ2) genus of the γ-herpesviridae subfamily of herpesviruses. The structure of the KSHV capsid purified from BCBL-1 cells induced with TPA is shown in Figure a (the image was kindly provided by Z. Hong Zhou. Data were taken from [88]). It is the eighth and most recently identified human herpesvirus (thereby designated HHV-8). Close homologues of KSHV have been identified in chimpanzees, gorillas and rhesus macaques and phylogenetic analysis has indicated that it shares substantial genetic homology with the *Rhadinovirus* Herpesvirus Saimiri (HVS), found in *Saimiri sciureus* [43, 70, 73]. The closest human relative of KSHV is the gammaherpesvirus Epstein-Barr Virus (EBV), genus *Lymphocryptovirus* (γ1) [55].