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EDITORIAL

KAPOSI SARCOMA UPDATE: CLINICAL-MOLECULAR CORRELATIONS*

Since the 1960s, research on the endothelial tumor known as Kaposi sarcoma (KS) has indicated that KS shares little in common with a true human sarcoma. KS arises in a multicentric pattern with each lesion showing a chronological progression to the spindle cell stage. Among the other most significant features of KS are:

1. All KS is caused by human herpesvirus 8 (HHV8 or KSHV) (1-3).
2. Each spindle cell KS lesion contains a latent-lytic HHV8 infection (4).
3. Immunodeficiency is the sole *known* modulator of KS induction and growth clinically (5,6).
4. The pattern of expression and retention of basement membrane proteins are inconsistent with a metastasizing neoplasm (7-9).
5. Lesions show a mixed endothelial-lymphendothelial phenotype with shunting between both vascular networks (8,10).

KSHV

KSHV is an approximately 170 kb γ-herpesvirus with tropism for human endothelium and B lymphocytes. In immunodeficient persons, at least, it may reside in other cells, such as monocytes and prostatic epithelium. KSHV is detected in nearly all cases of KS, irrespective of clinical setting. Seroconversion confers a high risk of developing KS in patients with HIV. The mode of transmission in immunodeficient patients is personal contact, possibly sexual contact, but it is not known how persons with classical KS contract KSHV. In several countries, the age-related incidence of KSHV infection slowly rises as people approach middle-age, much unlike the situation with other human herpesviruses. Overall seropositivity in Western countries is 1-5%.

Most endothelial cells in KS harbor the virus as latent intranuclear episomes, whereas less than 2% of nuclei express lytic phase transcripts. Production of viral particles may conceivably allow recruitment of newly infected endothelial cells into the tumor.

Of all known human herpesviruses, KSHV contains the largest number of 'borrowed' homologues of mammalian genes (>10), and these code for cytokines, signal transduction proteins, regulators of the cell cycle and apoptosis. Transfection assays have confirmed that several genes have angiogenic properties, but the molecular pathways leading to the *specific* pathological characteristics of KS are as yet unknown.

PRIMACY OF IMMUNODEFICIENCY IN KS INDUCTION

The relation between immunodeficiency and KS has been known since the 1940s. Recent studies have shown that KS induction occurs at a linear rate of ~3-5% per yr after

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KSHV seroconversion in HIV-infected patients. This compares with ~4% per yr in seroconverted renal transplant patients (after 2 yrs of followup). In other words, two different challenges to the immune system, HIV infection and therapeutic immunosuppression, are associated with similar rates of KS induction in patients for whom KSHV seroconversion can be accurately pinpointed. These observations fail to support contentions that the HIV *tat* protein is a modulator of KS.

BASEMENT MEMBRANES: KS VS. ANGIOSARCOMA

A major and possibly unique feature of KS is the consistent, strong immunoreactivity for the major basement membrane (BM) macromolecules laminin, collagen IV and fibronectin, which enmesh single or double CD31-positive spindled endothelial cells, despite the paucity of visible BM in the electron microscope. In marked contrast, post-mastectomy cutaneous angiosarcoma (Stewart-Treves syndrome), shows only randomly preserved stretches of these immunoreactive proteins in concordance with scattered ultrastructurally visible segments of BM. In angiosarcoma—similar to other metastasizing sarcomas and carcinomas—such changes are indicative of the activity of matrix metalloproteinases, but the action of these enzymes in KS is unclear. Only perlecan has been shown to be lacking in KS basement membrane. It is possible that this accounts for the lack of ultrastructural BM, as perlecan knockout mice have also been shown to lack ultrastructural BM in subsets of small blood vessels and in cardiac myocytes.

Importantly, each metachronous KS lesion displays the above BM phenotype, indicating that progressive loss of BM proteins does not occur with temporal progression. These findings (and others, including the stereotypical histological development of KS at any given site) strongly support the multicentric rather than metastatic character of Kaposi sarcoma.

MIXED ENDOTHELIAL PHENOTYPE

Morphologically, KS lesions begin as a proliferation of capillary-venule-sized vessels with dissecting lymphatic-like spaces, the latter also showing BM changes similar to those of spindled endothelium. Normal lymphatic skin capillaries show attenuated immunoreactivity for laminin and collagen IV, but lack fibronectin and perlecan, so that the BM alterations noted above also suggest a mixed lymphatic-blood vascular phenotype. Normal lymphatic capillaries tend not to express CD34, but do express CD31, both molecules being present in blood vessel endothelium. Both are also strongly expressed in KS endothelium.

The hybrid phenotype comprises presumably the biological basis for angiographically demonstrated shunting between the lymphatic and venous systems, which is morphologically best illustrated by the presence of 'radial veno-lymphatics' in deep veins.

CONCLUSION

Kaposi sarcoma is a prototype of disturbed endothelial differentiation in the microcirculation. This implies that the molecular pathways regulating the differentiation of veins and lymphatics may be defined partly by studying the interaction of KSHV products with molecular markers known to be involved in this differentiation process. The ultimate goal would be to exert exogenous control over this process, not only to halt the progression of lesions in KS patients, but also, for example, to be able to affect angiogenesis in tissue repair and neoplasia.

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