Kaposi sarcoma (KS) is distinct from other cancers in multiple ways. The most remarkable difference is that it first manifests itself as many distinct tumor lesions at discrete locations. KS is associated with HHV8 infection, whether it develops in the setting of HIV infection and concomitant use of immune-suppressive agents or in older men of Mediterranean descent. Another notable feature of KS is its regression upon withdrawal of immune suppressive agents (or improvement of immune status such as following HIV therapy). The unique characteristics of KS have raised questions as to its clonal nature and whether it is a true malignancy or a proliferative disorder not unlike that seen with Epstein-Barr virus (EBV) infection. Previous work to determine the clonal nature of KS used the polymorphic androgen receptor locus on the X chromosome. The basis of this approach is that in each female somatic cell, one copy of the X chromosome is permanently inactivated by DNA methylation, and the inactivation is preserved in all daughter cells. Random inactivation of either X chromosome in normal tissues results in nearly equal numbers of cells with either paternal or maternal X chromosome inactivation. In a population of tumor cells derived from a unique transformed cell, on the other hand, all cells show either paternal or maternal X chromosome inactivation. X chromosome–based analyses of KS lesions from women allowed previous investigators to determine if the tumor was clonal or oligoclonal. Results from one group indicated that KS is a clonal disease (1). In contrast, another group found that KS lesions were clonal in only a minority of the KS lesions. Furthermore, analysis of multiple lesions from individual patients showed that different lesions represented different clones, and the majority of the lesions were oligoclonal (2).

In this issue of the Journal, Duprez et al. (3) have extended this work by using a different method to examine the clonality of KS lesions. In an approach that is conceptually similar to one used in determining the clonality of EBV-associated lymphoproliferative disorders, it is possible to use the size heterogeneity of the viral fused terminal repeat region to determine the clonal nature of a population of infected cells. The HHV8 terminal repeat was investigated in KS tumor tissues from both men and women. Multiple biopsies from individual patients and a large number of biopsy samples revealed that there is evidence for KS lesions that are clonal, although these represent a minority of the tumors. Nearly 80% of the KS lesions were oligoclonal, with evidence of clonal and oligoclonal KS lesions within the same patient. Thus, KS is a multifocal disease, and all lesions do not arise from a single clone. Although whole KS lesions were studied, where infiltrating monocytes and B cells infected with HHV8 could potentially reduce the sensitivity of the assay, this is the largest study that has addressed the issue of KS clonality.

With some resolution as to the clonal nature of KS of the skin and lymph node, similar analysis remains to be done for visceral KS, which can be more invasive, leading at times to catastrophic organ dysfunction and even death. It is also not known if the clonal KS lesions identified in this study were more aggressive and less likely to respond to therapy.

Another area that requires further investigation is the role of endothelial cells in KS. KS tumor cells share many markers with vascular endothelial cells, and HHV8 can infect endothelial cells and induce KS-like spindle cell morphology in vitro. Furthermore, it has recently been shown that circulating endothelial precursor cells in patients with KS have evidence of HHV8 infection (4). The capacity of circulating endothelial precursor cells to integrate into newly forming vasculature raises an intriguing set of questions (5): Does KS develop following transmission of HHV8 from monocytes, B lymphocytes, or endothelial cells to dermal microvascular endothelial cells? Do tumor cells circulate and contribute to the HHV8-infected circulating endothelial precursor cell pool? Alternatively, do de novo HHV8-infected circulating endothelial precursor cells home to the permissive sites and propagate to produce KS lesions? Regardless of the source of HHV8-infected circulating endothelial cells, do these cells acquire an enhanced proliferative or transformed phenotype? Answers to these questions may further our understanding of KS pathogenesis and the identification of potential novel targets for intervention.

References


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