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Characterization of lytic human herpesvirus-8 gene expression in Kaposi sarcoma tumor tissue and its clinical correlates

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Background

Human herpesvirus 8 (HHV-8) replication is necessary for KS tumor growth and maintenance, and the detection of replicating HHV-8 in the peripheral blood predicts the development of KS [1]. Quantities of HHV-8 lytic and latent mRNA vary in KS biopsy tissue [2,3], suggesting that differences in lytic gene expression may be important in tumor pathogenesis and could have clinical significance. We evaluated lytic and latent mRNA transcripts in KS tumors from Ugandans with epidemic KS, and examined associations between HHV-8 gene expression in tumors, KS morphology, and systemic viral replication.

Methods

KS biopsy specimens were obtained from 13 treatment-naive, HIV-positive Ugandans with histologically confirmed KS. Participants also collected oral swabs daily and plasma samples weekly over 4 weeks to quantify HHV-8 replication. HHV-8 mRNA gene transcripts, including 2 lytic genes (K8 and ORF50) and 1 latent gene (ORF73), and GAPDH were quantified in biopsy specimens using RT-PCR; total RNA was determined by optical density. Only specimens with total RNA >10 ng and GAPDH threshold cycle (Ct) <35 were included in the analysis. HHV-8 mRNA log copies were normalized to the total ng of RNA in samples.

Results

HHV-8 mRNA gene transcripts were detected in all 13 KS biopsy samples. In all samples, the quantity of mRNA from lytic genes (K8 or ORF50) exceeded that of ORF73 when adjusted for total RNA recovered, though in two samples the amount of ORF73 mRNA exceeded the amount of ORF50 mRNA. The quantity of HHV-8 mRNA detected was highly correlated within samples (K8 and ORF50 Spearman coefficient (Sp)=0.92; K8 and ORF73 Sp=0.78; ORF50 and ORF73 Sp=0.84). Tumors of nodular morphotype had a lower proportion of lytic genes detected compared to macular morphotype (K8/ORF73 p=0.04; ORF50/ORF73 p=0.07). The quantity of K8, ORF50, and ORF73 mRNA in KS biopsies was positively associated with the detection of oral HHV-8 (K8 p=0.003; ORF50 p<0.001; ORF73 p=0.002). The quantity of lytic K8 and ORF50 mRNA, but not latent ORF73 mRNA, was also positively associated with the quantity of HHV-8 detected in saliva (K8 p=0.06; ORF50 p=0.06).

Conclusions

KS tumors in our cohort express a preponderance of lytic HHV-8 gene products. The quantity of lytic HHV-8 mRNA detected in KS tumors is associated with tumor morphotype and the detection of replicating HHV-8 in the oropharynx. Quantification of HHV-8 mRNA from KS tissue may provide insight into the pathophysiology of KS and could help predict disease progression and response to treatment.

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