

Poster presentation

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## Cellular gene regulation by K13/vFLIP of Kaposi's sarcoma-associated herpesvirus

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*ORFK13/vFLIP* of Kaposi's sarcoma-associated herpesvirus (KSHV) encodes a 188-amino acid protein, which binds with I $\kappa$ B kinase gamma subunit (IKK $\gamma$ ) to activate the NF $\kappa$ B pathway. To gain insight into the changes induced by K13 in endothelial cells, we retrovirally expressed *ORFK13* in human umbilical vein endothelial cells (HUVECs) and examined by DNA microarray patterns of genes expression in control retrovirus- and K13 retroviral-infected HUVECs. As expected, expression of numerous NF $\kappa$ B-targeted genes increased and expression of a limited number of genes decreased in K13-expressing HUVECs compared to control. Genes with increased expression included pro-inflammatory chemokines, cytokines, and adhesion molecules. Consistent with these results, K13-expressing HUVECs promoted monocyte attachment *in vitro* more effectively than controls, an observation consistent with immunofluorescent staining of AIDS-KS tissue showing infiltration of CD68-positive monocyte/macrophages. These infiltrating CD68-positive cells displayed moderate expression of VEGF, suggesting that K13 expression in KSHV-infected cells contributes to monocyte/macrophages attachment and represents a source of VEGF for tumor cells. Additionally, retroviral gene expression of *ORFK13* caused a dynamic morphological change in HUVEC that turned into spindle-like cells, and altered endothelial formation of vascular structures on extracellular matrix. In another aspect, K13 retrovirus induced significant expression of human thymidine phosphorylase, which is also called platelet-derived endothelial cell growth factor (PD-ECGF). PD-ECGF can

metabolize 5-fluoro-5-deoxyuridine (5-dFUrd) into 5-fluorouridine (5-FU), a thymidylate synthase inhibitor. When cytotoxicity was measured, 5-dFUrd selectively killed K13-expressing HUVECs at low concentrations (0.1–1  $\mu$ M), which did not affect the survival of control HUVECs. This observation has potential clinical implications for the treatment of KSHV-related malignancies where *ORFK13/vFLIP* is expressed and responses to current therapy are poor.