Infectious Agents and Cancer

Poster presentation

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 Iκb kinase gamma subunit (IKKγ) to activate the NFκB 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 NFκB-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 cytotoxity was measured, 5-dFUrd selectively killed K13-expressing HUVECs at low concentrations (0.1–1 μM), 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.