Flavopiridol inhibits angiogenic properties of Kaposi’s sarcoma-associated herpesvirus encoded G-protein coupled receptor


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Kaposi’s sarcoma-associated herpesvirus (KSHV/HHV8) has been identified as the etiologic agent of Kaposi’s sarcoma (KS). In its most aggressive form, KS is a multifocal highly vascularized neoplasm that is the most common malignancy associated with acquired immunodeficiency syndrome (AIDS). Although highly active anti-retroviral therapy has decreased the incidence of KS, it remains an incurable tumor for which there is no established treatment. Due to the vascular nature of KS, an anti-angiogenic therapeutic approach is attractive. Recent evidence suggests that inhibition of P-TEFb, a transcriptional elongation factor composed of cyclin dependent kinase 9 (CDK9) and its regulatory partner cyclin T, is anti-angiogenic.

Experimental evidence suggests that the KSHV-encoded G-protein-coupled receptor (vGPCR) is required and sufficient to initiate angiogenesis and tumorigenesis. Expression of vGPCR in endothelial cells has been shown to induce the secretion of an array of growth factors and cytokines including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), both potent pro-angiogenic factors that enhance endothelial cell survival. We have also shown that expression of vGPCR in endothelial cells upregulates expression of the anti-apoptotic gene Bcl-2 and enhances their survival upon serum starvation. We hypothesized that flavopiridol, a novel inhibitor of CDK9, would inhibit vGPCR-induced angiogenesis by downregulating expression of angiogenic growth factors and/or Bcl-2.

Using primary human umbilical vein endothelial cells (HUVEC) transduced with either a control or a vGPCR-expressing retroviral vector, we demonstrate that CDK9 is directly activated upon vGPCR expression. vGPCR-expressing HUVECs also show significantly enhanced ability to form capillary-like tubules on growth factor-reduced Matrigel as well as enhanced migration towards chemotactic stimuli. Treatment with 50nM flavopiridol prior to and during the migration and tubule formation assays inhibited the vGPCR-enhanced formation of tubules and reduced their migration ability. These results correlated with a significant decrease in expression of VEGF-A, VEGF-C and Bcl-2 mRNA. Together these results suggest that P-TEFb plays a role in mediating transcriptional regulation of vGPCR responsive genes and implicate CDK9 as a potential target to reduce vGPCR-enhanced endothelial cell survival, angiogenesis and tumorigenesis. Experiments are currently underway to determine whether inhibition of P-TEFb activity suppresses KSHV-enhanced angiogenesis and tumorigenesis in vivo.