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The angiogenic properties of Kaposi's sarcoma-associated herpesvirus encoded G-protein coupled receptor are reduced by flavopiridol, an inhibitor of cyclin-dependent kinase 9

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Kaposi's sarcoma-associated herpesvirus (KSHV/HHV8) has been identified as the etiologic agent of Kaposi's sarcoma (KS), a multifocal highly vascularized neoplasm that is the most common malignancy associated with AIDS. Although highly active antiretroviral 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. The KSHV-encoded G-protein-coupled receptor (vGPCR) is required and sufficient to initiate angiogenesis and tumorigenesis. 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.

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. To test this hypothesis, in vitro and in vivo angiogenesis assays were carried out using primary human umbilical vein endothelial cells (HUVECs) transduced with either a control or a vGPCR-expressing retroviral vector and then treated with flavopiridol. Our results show that CDK9 activity is increased in vGPCR-expressing HUVECs and that pretreatment with 50 nM flavopiridol inhibited vGPCR-induced migration and capillary tubule formation. These results correlated with a significant decrease in expression of genes encoding the angiogenic factors VEGF-A and VEGF-C and the pro-survival factor Bcl-2. Initial studies to determine the molecular mechanisms by which CDK9 affects angiogenesis demonstrated that HUVECs treated with bFGF and VEGF had increased CDK9 activity as well as increased expression of the major isoform of $Cdk9_{42}$ and cyclin T. Although Cdk9 was described in the literature as a general transcription factor, we have observed that inhibition of CDK9 by flavopiridol decreased the expression of Bcl-2 but not p21 in HUVEC. Together these results suggest that CDK9 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 under way to determine whether CDK9 is directly activated upon vGPCR expression and whether inhibition of CDK9 activity suppresses KSHV-enhanced angiogenesis and tumorigenesis in vivo.

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