Kaposi's Sarcoma-Associated Herpesvirus (KSHV) G-Protein Coupled Receptor (vGPCR) Enhances Endothelial Cell Survival

Elizabeth R. Abboud¹, Magdalena Angelova¹, Marybeth Ferris¹, Bryan D. Shelby², Anne B. Nelson¹, Joseph A. Lasky³, Cindy A. Morris¹ and Deborah E. Sullivan¹

¹Tulane University School of Medicine, Department of Microbiology and Immunology, New Orleans, LA. ²Centers for Disease Control and Prevention, NCIRD/DVD/MMRHLB/Herpesvirus Team, Atlanta, GA. ³Tulane University School of Medicine, Department of Medicine, New Orleans, LA.

The virally encoded KSHV vGPCR is a constitutively active lytic phase protein with significant homology to the human interleukin-8 (IL-8) receptor. It has been shown that the KSHV vGPCR is necessary and sufficient to induce angiogenesis as well as the spindle shaped morphology characteristic of Kaposi's Sarcoma (KS) lesions. Studies conducted by our lab have previously shown that Bcl-2, an anti-apoptotic protein, is upregulated in spindle-shaped endothelial cells, the main component of KS lesions.

In the study presented here, endothelial cells expressing vGPCR showed increased survival after induction of apoptosis by serum-starvation. Microarray analysis of cells expressing vGPCR revealed increased levels of Bcl-2, Bcl-2A1 and BIRC3 mRNA and these results were validated by quantitative real-time PCR. Moreover, siRNA inhibition of Bcl-2 led to a partial loss of the vGPCR-induced survival advantage. An increase in Bcl-2 protein levels was found when vGPCR was expressed in endothelial cells. The vGPCR-induced increase in both Bcl-2 mRNA and protein levels was dependent on PI3K/Akt; however, inhibition of mTOR with rapamycin did not affect vGPCR-induced Bcl-2 protein levels. Collectively, the results of this study identify Bcl-2 as a mediator of vGPCR-induced endothelial cell survival, and that Bcl-2 is a downstream effector of Akt in this process. We are currently working to identify whether A1 works in concert with Bcl-2 to prevent apoptosis in endothelial cells.