

KSHV-ENCODED MICRO-RNAS AND THEIR POTENTIAL ROLE IN VIRAL BIOLOGY AND PATHOGENESIS

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MicroRNAs are small, non-coding RNAs that post-transcriptionally regulate gene expression by binding to 3'UTRs of target mRNAs. Kaposi's sarcoma-associated herpesvirus (KSHV), a virus linked to malignancies including KS and primary effusion lymphoma (PEL), encodes 12 miRNA genes but only a few regulatory targets are currently known. Using ectopic expression of viral miRNAs in combination with gene expression profiling, we identified miRNA targets, including THBS, a strong anti-angiogenic factor, and several genes involved in regulation of apoptosis and proliferation.

In addition, we found that KSHV-miR-K12-11 shares 100% seed-sequence homology with hsa-miR-155, a miRNA frequently found up-regulated in lymphomas and critically important for B-cell development. Based on this seed-sequence homology, we hypothesized that both miRNAs regulate genes that are essential for terminal B-cell differentiation and as a result, KSHV-miR-K12-11 may mimic hsa-miR-155. Previously, our lab and others have published that ectopic expression of either miRNA inhibited expression of a BACH-1 3'UTR luciferase reporter, indicating that both miRNAs can indeed regulate identical gene targets (1, 2).

Using bioinformatic approaches in combination with 3'UTR reporter assays, we found that CEBP/ β and PU.1 are both targets for miR-K12-11 and miR-155. Because CEBP/ β and Pu.1 have been shown to play essential roles in terminal B-cell differentiation, we suggest that viral miRNA mimics miR-155 in order to regulate post-germinal center differentiation of B-cells. Ongoing experiments to directly evaluate the effects of KSHV-miR-K12-11 expression on B-cell differentiation, as well as miRNA profiling studies in endothelial cells, will also be discussed.

1. Skalsky, R.L., Samols, M.A., Plaisance, K.B., Boss, I.W. et al., *Journal of Virology*. 2007. 81(23): 12836-12845.
2. Gottwein, E., Mukherjee, N., Sachse, C., Frenzel C. et al., *Nature*. 2007. 450(7172): 1096-1099.