

Bankhead-Coley Cancer Research Program

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Project Title: Activation of the ERK/RSK MAPK Pathway by KSHV

Project Summary: Tumor viruses account for about 15 percent of human cancers. Kaposi's sarcoma associated herpesvirus (KSHV) is such a tumor virus; it causes Kaposi's sarcoma (KS), primary effusion lymphoma, and multicentric Castleman's disease. KS development is well documented to require recurrent episodes of lytic KSHV replication, so blocking viral replication could prevent or cure KSHV-related human cancers. One way to inhibit KSHV replication is to disrupt cellular signaling, which viruses rely on for their replication. A common cellular signaling pathway called extracellular signal regulated kinase (ERK) MAPK is activated by KSHV and plays a pivotal role in KSHV lytic replication, but the mechanism and the viral factor responsible are unknown. We recently found that a KSHV protein called ORF45 interacts with cellular kinases called RSK1 and RSK2 and strongly stimulate their enzyme activities. RSKs are direct substrates and functional mediators of ERK. Activation of RSK by ORF45 requires ERK but not activation of MEK, a kinase that functions "further upstream" in the process. RSK and ERK are activated with similar kinetics during KSHV infection. We further showed that ORF45 contributes significantly to the sustained ERK activation during KSHV replication. Importantly, depletion of RSK or inhibition of RSK activity with an inhibitor specific to it strongly suppresses KSHV lytic replication, suggesting that ERK/RSK signaling can be a useful target for anti-KSHV intervention. In this grant, we will characterize the mechanism of ERK/RSK activation and its role in viral lytic replication and pathogenesis. Results from this research may lead to a novel therapeutic approach to KSHV-related human cancers.