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The Kaposi's sarcoma-associated herpesvirus E3 ubiquitin ligase K5 acts as a novel oncogene, altering cellular metabolism and signaling: implications for tumorigenesis

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While it is clear that Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8) is the causative agent of a number of malignancies including multicentric Castleman's disease, primary effusion lymphoma, and Kaposi's sarcoma (KS), the molecular mechanisms of tumor induction by this virus are still unclear. In part, KS lesion presentation is thought to be driven primarily through paracrine mechanisms and is mainly observed in immunocompromised patients. Monocyte subsets, including dendritic cells and macrophages, are crucial to immune system functionality and are also skewed in KS patients. The goals of this study were to investigate a potential role for the E3 ubiquitin ligase K5 of KSHV, which plays a role in viral immune evasion, in altering monocyte functionality, thereby contributing to KSHV-driven tumorigenesis.

A series of wild-type (WT) and mutant K5-expressing stable cell lines were generated in THP-1 monocytic cell line and examined. Surprisingly, these cells demonstrated a serum-dependent increased growth rate and a propensity to acidify the growth medium as compared to vector-THP-1 cells. Biochemical examination indicated that K5 induced aerobic glycolysis and other hallmarks of the "Warburg Effect," including increased lactate production and glucose uptake. Observed increases in Akt and total cellular tyrosine phosphorylation, combined with the serum-dependence, suggested a role for receptor tyrosine kinases (RTKs). A human-RTK array demonstrated increased activation of the Flt-3, Axl, PDGFR-ß, and Flt-4 receptors in K5-expressing versus vector cell lines. Subsequent testing demonstrated increased sensitivity of K5-expressing THP-1 cells to growth arrest and apoptosis by sunitinib and increased ligand-dependent signaling. Dynamin inhibitor studies showed that K5 can target these RTKs from the surface to increase intracellular signaling. Additional molecular details will be presented.

Overall, our studies demonstrate that the KSHV K5 protein is acting as a novel oncogene – the first viral protein of its kind – to drive monocyte subset expansion and alter cellular metabolism, contributing to a pro-tumorigenic microenvironment. Intriguingly, the metabolic changes observed are caused by a single KSHV protein and thus serve as a useful model to study different aspects of KS pathology and its overall regulation of cellular metabolism. These studies also provide additional rationale for the currently ongoing clinical trials of sunitinib, Gleevec, and rapamycin for the treatment of KSHV-driven neoplasias. Finally, the ability of this viral E3 ubiquitin ligase to drive metabolic changes provides the tantalizing suggestion that a cellular ligase may be acting in a similar, either physiologic or oncogenic, manner.

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