A whole genome approach to better understand the link between Kaposi’s sarcoma-associated herpesvirus and human cancers

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Aim/Background: Kaposi’s sarcoma (KS) and primary effusion lymphoma (PEL) are two human cancers caused by Kaposi’s sarcoma-associated herpesvirus (KSHV). These virally-induced malignancies are particularly likely to develop in the context of weakened immune systems. KS has become one of the most frequently reported cancers in parts of Africa, where HIV and KSHV are widespread. Both KS and PEL arise in settings of relatively low oxygen concentrations (hypoxia) and hypoxia can activate KSHV production. Also, KSHV can activate aspects of the cellular response to hypoxia. A whole genome approach was undertaken to investigate the genes that may be affected by hypoxia in KSHV-infected cells in order to determine the degree to which hypoxic pathways are utilized by KSHV and may affect the development of KSHV-associated cancers.

Methods: We addressed the question of microRNA (miRNA) and mRNA regulation through hypoxia by deep sequencing, gene expression and transfection assays of KSHV-infected cells (SLKK and BCBL1) and uninfected cells (SLK).

Results: We showed that (i) hypoxia changes both cellular mRNAs and miRNAs – but not viral miRNAs – in KSHV-infected cells, (ii) miR-210, a human miRNA involved in hypoxia and cancer, was increased by both KSHV infection and hypoxia, and may play a role in viral carcinogenesis, and (iii) cellular gene expression (mRNA) responses to hypoxia and KSHV infection are remarkably similar (~30%).

Conclusions: These results suggest that KSHV harnesses a part of the hypoxic cellular response and utilizes miR-210 up-regulation to its advantage. This is the first report of a hypoxia study using miRNA and mRNA-sequencing technique on pathogen-infected cells. The discovery of these miRNAs, genes, and pathways regulated by hypoxia and/or KSHV infection are essential to better understand the biology of KSHV-associated cancers.

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