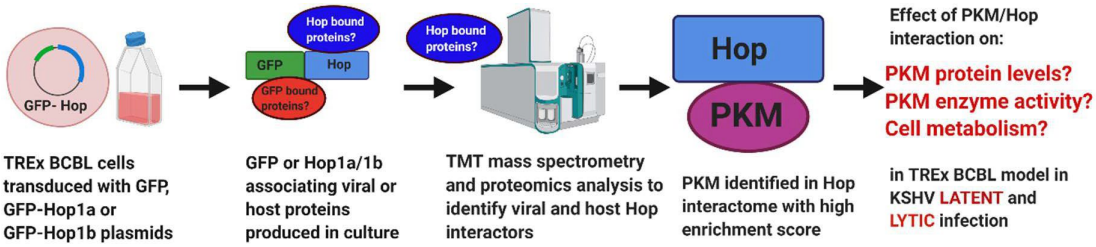
Hop mediated regulation of PKM and cellular metabolism in KSHV infection

Kirigin, E., Jackson, Z., Whitehouse, A. and Edkins, A.L.

Rhodes University: Biomedical Biotechnology Research Unit (BioBRU)



Introduction: Kaposi sarcoma-associated herpesvirus (KSHV) is prevalent in sub-Saharan Africa and is the causative agent of certain lymphomas and Kaposi sarcoma, a skin cancer which commonly occurs in AIDS patients. The virus demonstrates a biphasic lifecycle of unreactive latency and lytic infection. The human host co-chaperone Hsp70-Hsp90 organising protein (Hop) plays a role in the cellular stress response and is prominent in the cancerous phenotype. Hop1b is the canonical Hop isoform that has been the focus of all published studies to date, but recent work in our group has identified the novel Hop1a isoform. Importantly, chaperone and co-chaperone proteins such as Hop are utilised by viruses such as KSHV upon infection.

Methods: Global proteomics analysis of Hop1a and Hop1b immunoprecipitates from primary effusion lymphoma (PEL) cell lines undergoing KSHV lytic replication (TREx BCBL) revealed a cohort of glycolytic proteins that were enriched in complex with Hop compared to the unreactivated latent counterparts. Within this cohort, we selected the pyruvate kinase muscle isoforms 1 and 2 (PKM1 and PKM2) for further study, as PKM2 is an Hsp90 client and is implicated in KSHV infection.

Results: We validated the direct interaction between the PKM and Hop isoforms *in vitro* using purified proteins. In KSHV infected cells undergoing both latent and lytic replication, Hop 1a and Hop1b overexpression increased PKM2 protein expression levels and activity, and increased cellular metabolism by enhancing lactate production. In addition, PKM2 levels and enzyme activity were greater in KSHV infected lymphoma cells compared to a non-infected lymphoma cell line, which correlated with an enhanced metabolic rate.

Conclusions: Our data indicate that, during KSHV infection, Hop can associate with PKM and may reprogram host cell metabolism to resemble a more oncogenic phenotype. Hop may therefore be a drug target candidate to eradicate KSHV and prevent viral malignancies.

References:

Baquero-pérez, B., & Whitehouse, A. (2015). Hsp70 Isoforms Are Essential for the Formation of Kaposi ' s Sarcoma-Associated Herpesvirus Replication and Transcription Compartments. PLOS Pathogens, 11, 1–42.

Bhattacharya, K., Weidenauer, L., Luengo, T. M., Pieters, E. C., Echeverría, P. C., Bernasconi, L., Wider, D., Sadian, Y., Koopman, M. B., Villemin, M., Bauer, C., Rüdiger, S., Quadroni, M., & Picard, D. (2020). The Hsp70-Hsp90 co-chaperone Hop/Stip1 shifts the proteostatic balance from folding towards degradation. Nature communications, 11, 5975.

Dayton, T. L., Jacks, T., & Vander Heiden, M. G. (2016). PKM2, cancer metabolism, and the road ahead. EMBO reports, 17, 1721–1730.

Ma, T., Patel, H., Babapoor-Farrokhran, S., Franklin, R., Semenza, G. L., Sodhi, A., & Montaner, S. (2015). KSHV induces aerobic glycolysis and angiogenesis through HIF-1-dependent upregulation of pyruvate kinase 2in Kaposi's sarcoma. Angiogenesis, 18, 477–488.

Wen, K. W., & Damania, B. (2010). Hsp90 and Hsp40 / Erdj3 are required for the expression and anti-apoptoticfunction of KSHV K1. Oncogene, 29, 3532–3544.

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