Repressosome formation and disruption regulates the KSHV latent-lytic switch

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Introduction

The etiological agent of Kaposi's Sarcoma, Kaposi's sarcoma associated herpesvirus virus (KSHV), is the most recently identified human tumour virus. KSHV has two distinct forms of infection, latent persistence and lytic replication. The switch between these phases is important as lytic replication plays an essential part in the pathogenesis and spread of KSHV infection. The KSHV ORF 50 protein is the key gene product which regulates viral lytic gene expression as sustained transient expression of ORF 50 in a KSHV-latently infected cell line leads to the stimulation of its own expression and consequently viral lytic replication. This implicates the ORF 50 protein as the molecular switch for reactivation and initiation of the KSHV lytic replication cycle.

We are currently investigating the host cell-ORF 50 interactions to further understand the role of KSHV ORF 50 in the latent-lytic switch. We have demonstrated that KSHV ORF 50 interacts with the cellular protein, Hey-1. Hey-1 functions as a transcriptional repressor, acting as adapter protein that binds to specific DNA binding sites within gene promoters, and subsequently recruits transcriptional repressosome complexes.

The interaction between KSHV ORF 50 and the transcriptional repressor protein Hey-1 is a particular intriguing one. Why would ORF 50 interact with a transcriptional repressor protein, given the role of ORF 50 in transcriptional activation and initiating the lytic replication cycle? However, we have shown that the Hey-1-ORF 50 interaction is an essential interaction playing a pivotal role in regulating the KSHV latent-lytic switch.

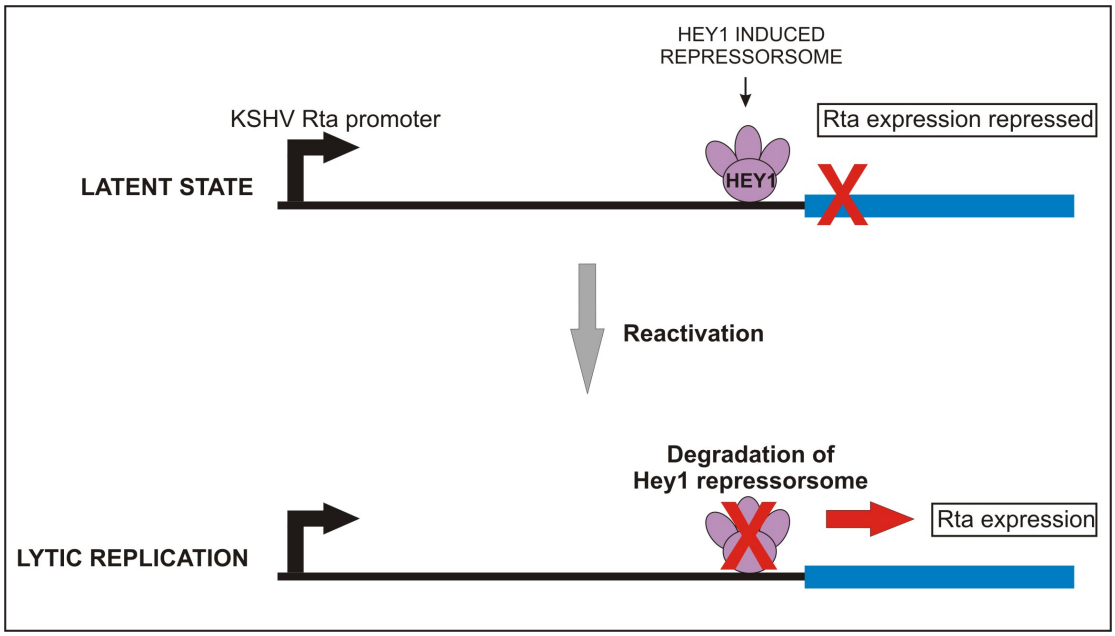

Figure: Repressosome assembly and disassembly regulates the KSHV latent-lytic switch

We have shown that Hey-1 specifically represses ORF 50 expression by binding the ORF 50 promoter and recruiting a functional repressosome, thus helping KSHV to remain in the latent state. However, we have also demonstrated that KSHV ORF 50 can act as an ubiquitin E3 ligase, which results in the degradation of Hey-1 via a proteasome-degradation pathway.

This disrupts the repressosome and allows ORF 50 expression leading to KSHV lytic replication.

We now aim to further characterise the DNA/protein and protein/protein interactions involved in KSHV reactivation and in the regulation of lytic gene expression. This analysis will also give further insights into the role of the cellular Hey-1 protein in transcriptional repression. Moreover, this project will provide valuable information on KSHV reactivation that may ultimately lead to the identification of specific antiviral targets to inhibit ORF 50–host cell interactions which may be developed as a novel treatment for this important human pathogen.

Publications

Wilson, S.J., Tsao, E., Webb, B.L., Ye, H., Dalton-Griffin, L., Tsantoulas, C., Gale, C.V., Du, D., Whitehouse, A. & Kellam, P. (2007). XBP-1 transactivates the KSHV ORF50 promoter, linking plasma cell differentiation to KSHV reactivation from latency. *Journal of Virology,* **81**, 13578-13586.

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