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Dendritic cell-mediated infection of primary B cells with KSHV

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Circulating B lymphocytes are the major reservoir of KSHV infection in infected subjects. However, B cell lines and primary B cells are resistant to direct KSHV infection *in vitro*. In addition, primary B cells are difficult to propagate for more than a few days. In this study, we combined a novel primary B cell propagation method with efficient infection mediated by dendritic cells to study KSHV *de novo* infection of primary B cells *in vitro*.

Primary monocyte-derived dendritic cells (MDDCs) or plasmacytoid dendritic cells (pDCs) were pulsed with KSHV for 4 hours at which point KSHV DNA was readily detectable. Uptake of KSHV was significantly reduced by pre-incubating cells with antibodies to integrins α3, β1 and DC-SIGN. Autologous B cells were grown on a feeder layer of irradiated NIH3T3 cells transduced with a human CD40L retroviral vector. KSHV+ DCs were co-cultivated with primary B cells for 4–8 hours and then separated by CD19+ immunomagnetic isolation. B cell cultures were maintained on feeder cells for >30 days and monitored for KSHV infection.

Efficient KSHV infection of primary B cells was mediated by both MDDCs and pDCs. KSHV LANA protein (ORF73) was detected by IFA in 2–15 percent of B cells through day 14. Viral gene expression analysis using a KSHV whole genome virus array showed establishment of latent KSHV infection followed by spontaneous reactivation of lytic viral replication in the primary B cell cultures.

These studies suggest that dendritic cells play an important role in the transmission and pathogenesis of KSHV in infected subjects as well as demonstrating a powerful *in vitro* model for studying KSHV infection of B cells.

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