25-HYDROXYCHOLESTEROL INHIBITS HERPESVIRUSES BY ACTIVATING INFLAMMATORY PATHWAYS

0256

Anna KP Serquiña[1], Takanobu A. Tagawa[1], Joseph M. Ziegelbauer[1]
1-HIV & AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA 20892

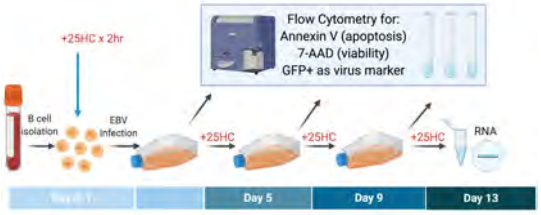
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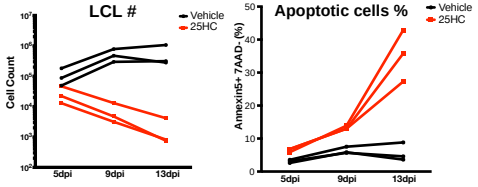
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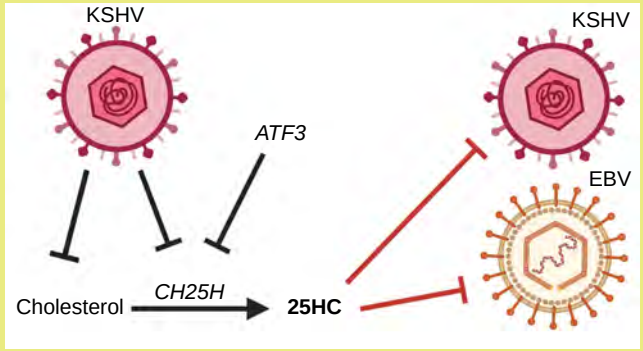
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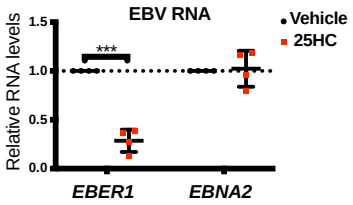
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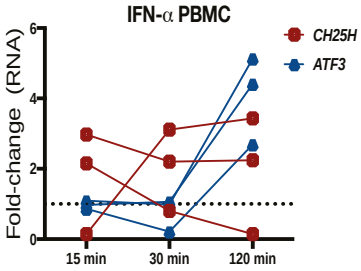


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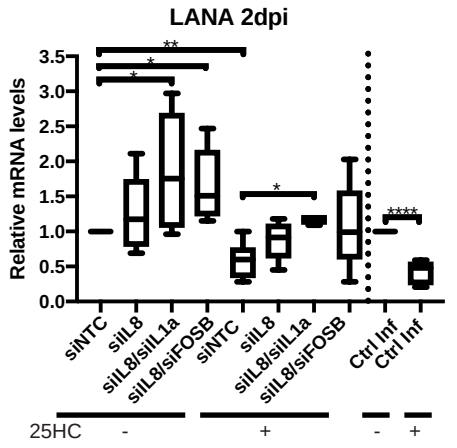


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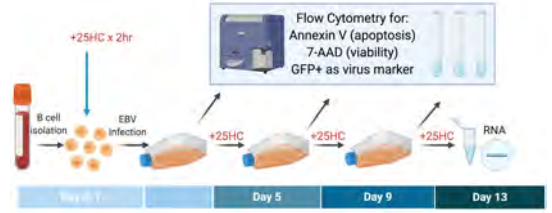
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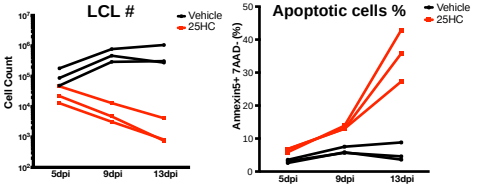
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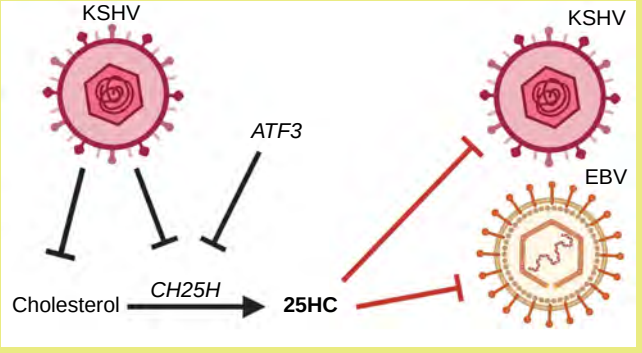
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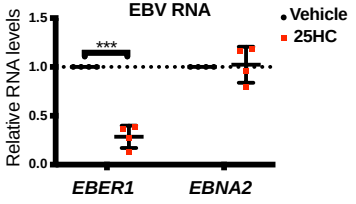
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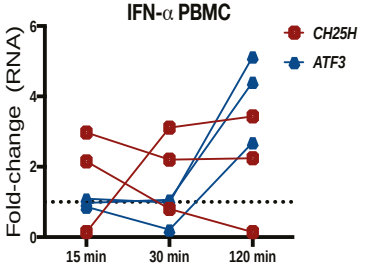




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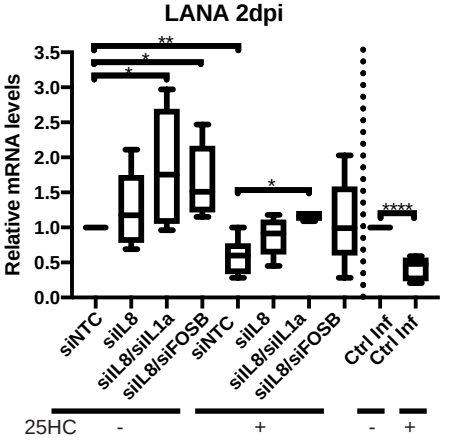
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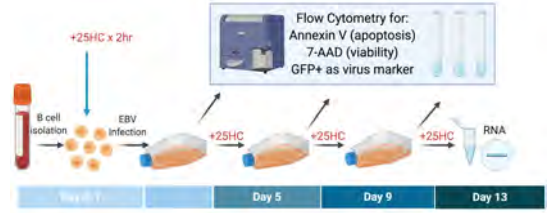
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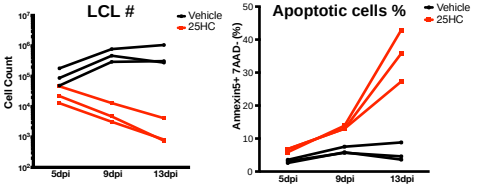
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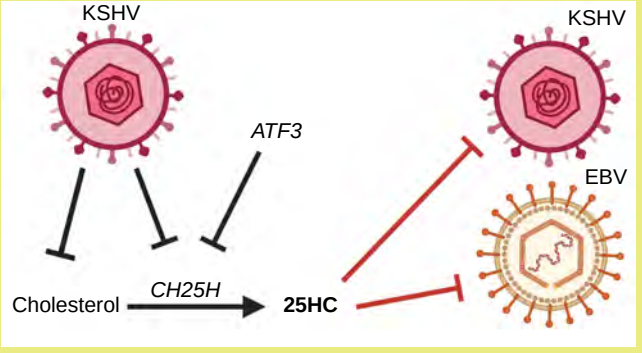
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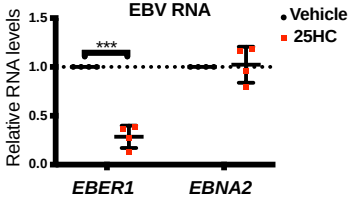
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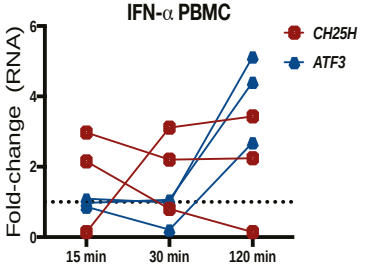




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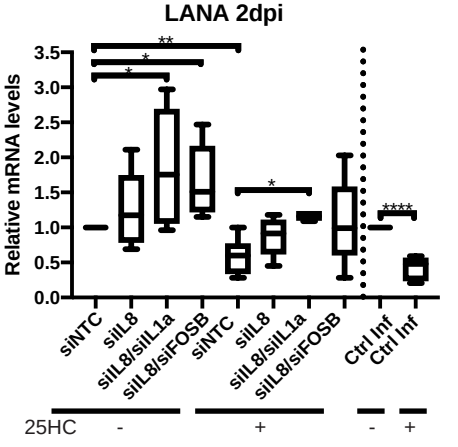
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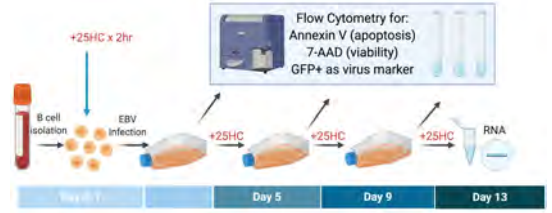
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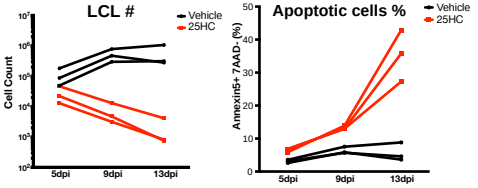
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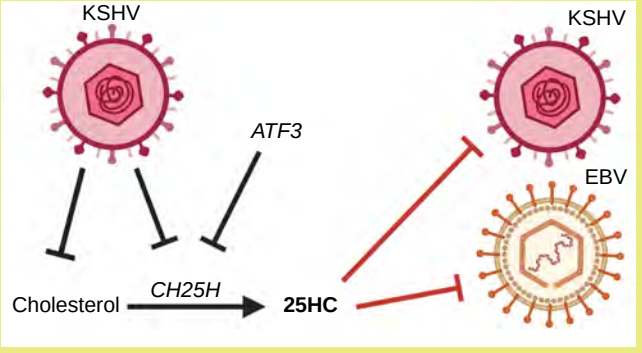
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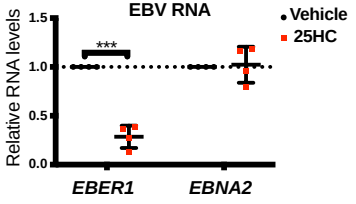
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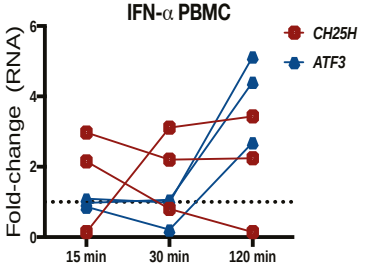




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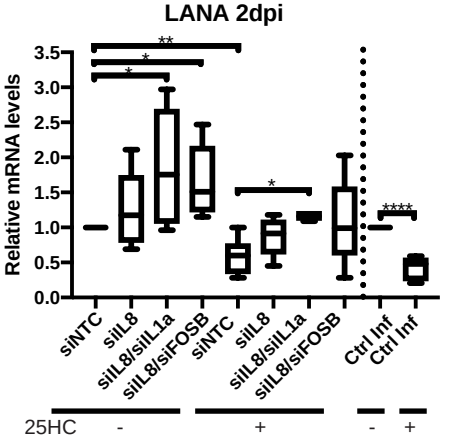
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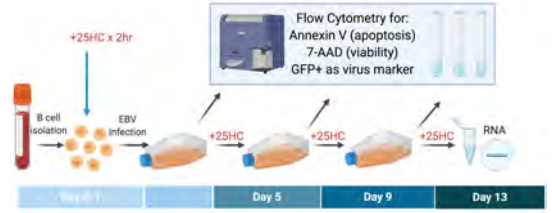
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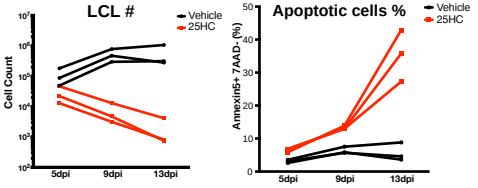
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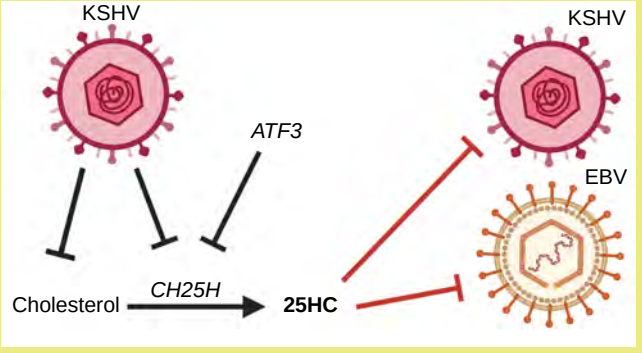
RESULTS

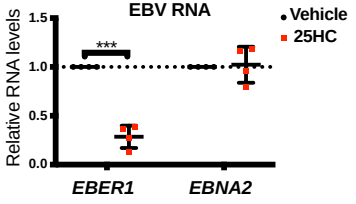
25HC is anti-proliferative and pro-apoptotic.



25-hydroxycholesterol blocks infection via inflammatory pathways and is antiviral against KSHV and EBV.

CH25H is interferon-inducible in PBMCs.

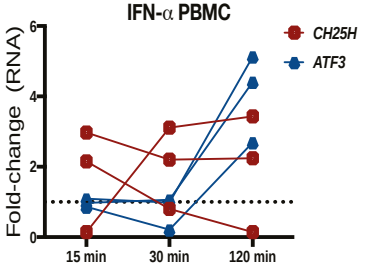




25HC represses EBER1 (ncRNA/RNA Pol III) but not EBNA2 (protein-coding/RNA Pol II) RNA expression.

• RNA from EBV-infected PBMCs (T-cell depleted) were harvested 2 weeks after infection

• RT qPCR for EBV viral transcripts (*ACTB* as reference gene)



CH25H is interferon (IFN)-inducible in PBMCs and ATF3 suppresses CH25H gene expression.

•RNA from PBMCs (3 volunteers) treated with IFN -α,-β, -γ at time points indicated

•Positive controls: *ISG15* and *IRF1* were induced

•IFN-α and -β induces *CH25H* in PBMCs, unlike HUVEC (Serquina mBio 2017); *GUSB* as reference gene

•*ATF3* (transcription factor that negatively regulates *CH25H* in HUVEC) transcript levels rise as *CH25H* expression plateaus or decreases

25HC induced several innate immunity genes (signaling, receptors) and pro-inflammatory factors in endothelial cells during KSHV infection.

•analysis of the subset of genes that are upregulated by 25HC in the context of infection showed enrichment of the following KEGG pathways:

KEGG Pathway	# Genes	adj pval -log10
Cytokine- cytokine receptor interaction	15	10.20
Rheumatoid arthritis	10	9.56
Pathways in Cancer	12	6.30
Malaria	5	4.39
Chemokine signaling pathway	7	3.70
Cell adhesion molecules	6	3.70
MAPK signaling pathway	8	3.70
Small cell lung cancer	5	3.52
JAK-STAT signaling pathway	6	3.40

Functional validation of candidate genes contributing to the 25HC antiviral effect.

•single and double siRNA knockdown of genes in the context of infection

•combinatorial knockdown required for recovery of virus (increase in LANA transcript)

•further work needed to map out the pathways that contribute towards the antiviral activity of 25HC

