Inhibition of Herpes Simplex Virus 1 (HSV-1) Replication by Inositol-Requiring Enzyme 1 (IRE1) Pathway

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Introduction

Endoplasmic reticulum (ER) plays important roles in viral replication. Viral infection can trigger ER stress. The ER stress is marked by the activation of a series of signaling pathways, called the unfolded protein response (UPR), which consists of three distinct, yet related, signal pathways, PRKR-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activated transcription factor 6 (ATF6). The PERK signaling branch has been the focus of investigation for its roles during HSV-1 replication. The bifunctional transmembrane kinase IRE1 is the most ancient in evolutionary terms and this signaling branch could affect cell fate during UPR. Studies have shown that IRE1 pathway is involved in many viral replication, such as Influenza A, Hepatitis C virus, Japanese encephalitis virus and Entervirus 71. However, little is known on the roles of IRE1 on HSV-1 infection. In this study we found that HSV-1 facilitates its replication by manipulating IRE1 signaling pathway through activating it's kinase activity and inhibiting RNase activity.

Materials and Methods

HeLa and HEC-1-A cells were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). HSV-1 (strain HF) was propagated and titrated on Vero cells as described previously (McLean et al., 1994).

Sodium tauroursodeoxycholate (TUDCA) and Thapsigargin (Tg) were purchase from Sigma (Sigma–Aldrich, Saint Louis, MO). Irestatin was purchase from MedChem Express (MedChemExpress).

Results

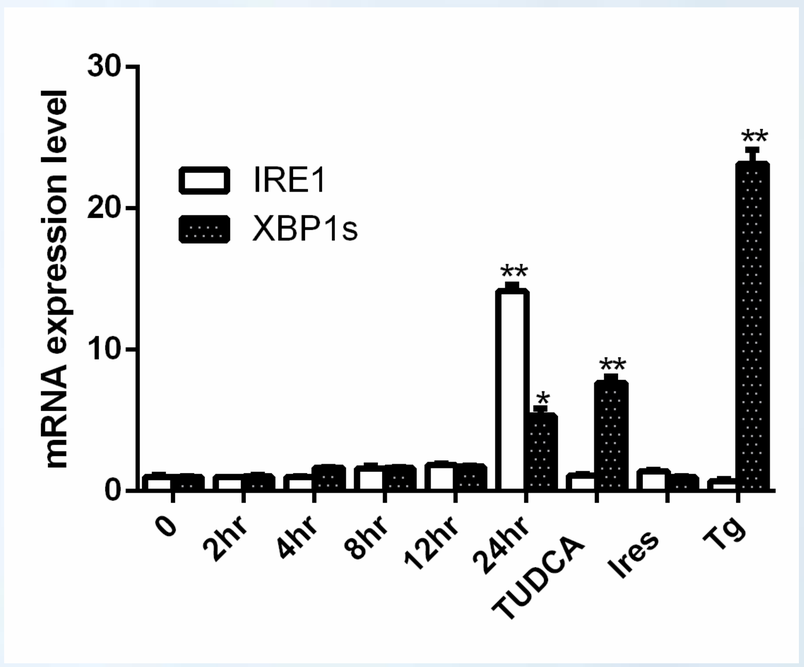

Fig. 1 IRE1 and XBP1s mRNA expression level in HSV-1 infected HEC-1-A cells.

The data shows that IRE1 branch of UPR is activated by HSV-1 infection 24hr p.i. We found that TUDCA can enhance the activity of IRE1/XBP1 signaling pathway. Tg is used as a positive control of ER stress activator and also improves the IRE1/XBP1 branch of UPR. As a inhibitor of RNase activity of IRE1, Irestatin does not induce the spliced XBP1 mRNA expression.

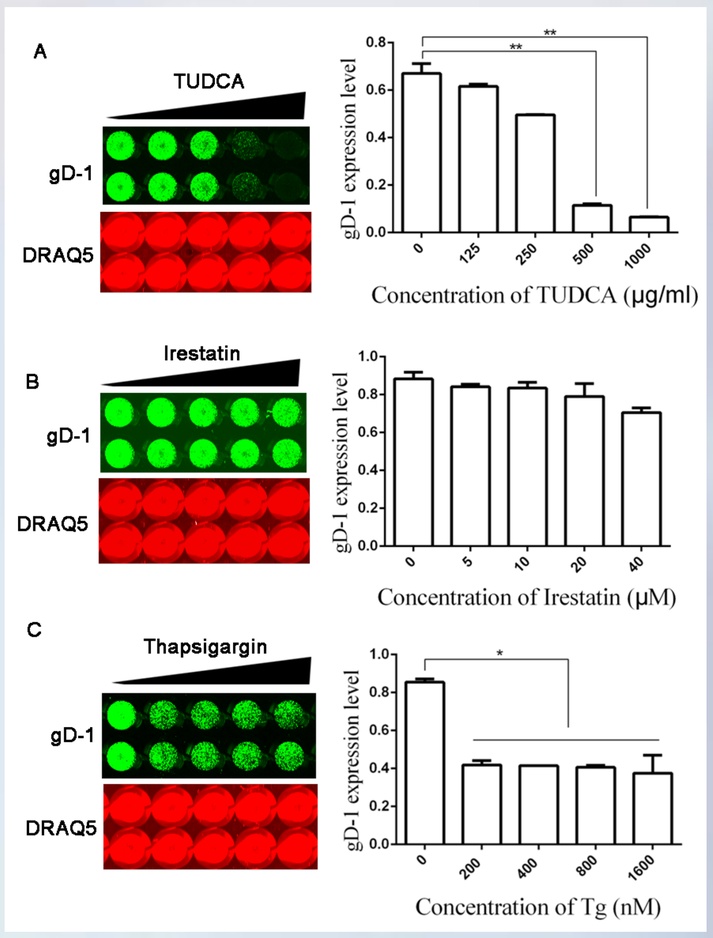

Fig. 2 Effect of TUDCA, Irestatin and Tg on HSV-1 replication

TUDCA and Tg inhibit HSV-1 infection significantly, but Irestatin can't. We speculate that there are some close ties between IRE1/XBP1 arm of UPR and HSV-1 viral replication.

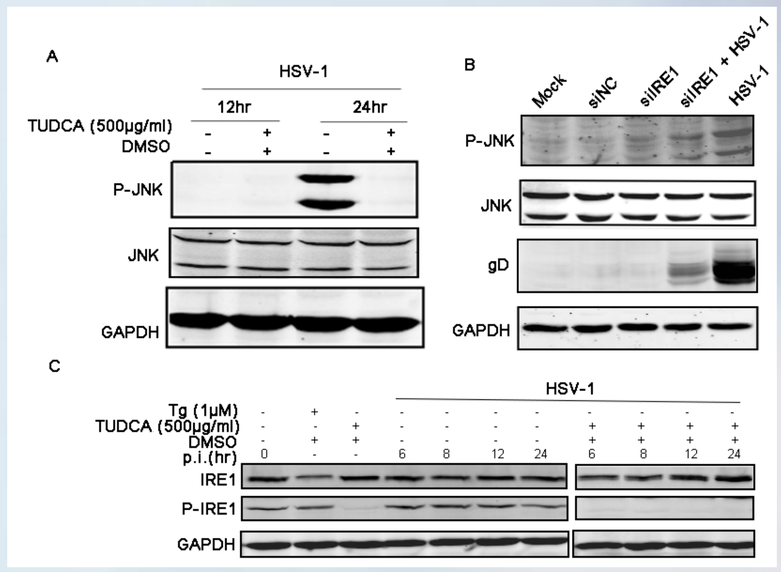

Fig. 3 Effect of TUDCA treatment and siIRE1 on JNK activation.

JNK activation is inhibited significantly by TUDCA (500 μg/ml) pretreatment or siIRE1. This result shows that IRE1/JNK signaling pathway is necessary for HSV-1 replication.

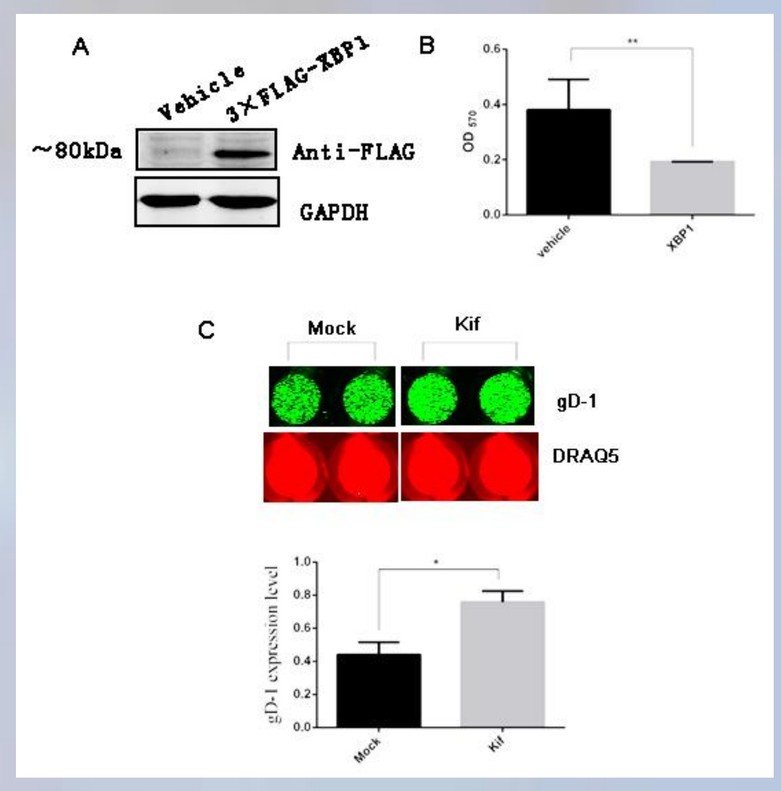

Fig. 4 Effect of XBP1 overexpression and inhibition of ERAD on HSV-1 replication.

HEC-1-A cells were infected with HSV-1/blue (moi=1) after XBP1s plasmid was transfected into cells in 24 hrs. The β-Gal activity is measured 12 hrs p.i. The result shows that HSV-1/blue replication is inhibited by XBP1s. ERAD is down-stream of XBP1. HSV-1 gene expression is increased by inhibiting ERAD (Fig 3C). This result indicates that it is unfavorable for viral replication to increase RNase activity of IRE1 .

Conclusions

1. HSV-1 facilitates its replication by manipulating IRE1 branch of UPR.
2. Enhancement of IRE1/XBP1 signaling pathway has an inhibitory effect on HSV-1 replication.
3. Investigation of viral components on the regulation of IRE1 activity is currently underway.

References

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Ozcan U, et al., 2006. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. Science **313:**1137-1140.