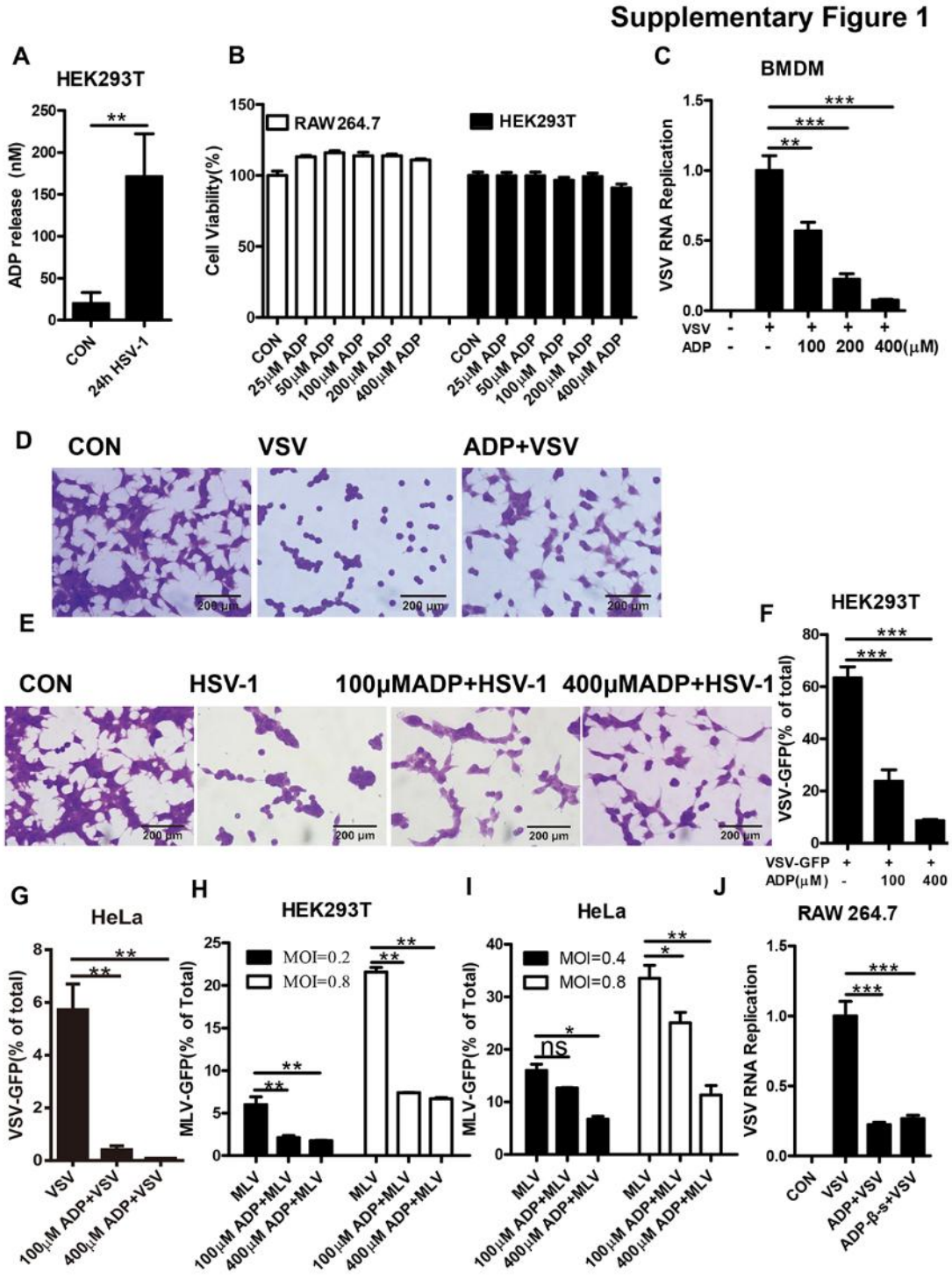
Supplementary Table S1 Primers used for Q-PCR

Genes	Primers(5′-3′)
β-actin	Forward: GTACGCCAACACAGTGCTG Reverse: CGTCATACTCCTGCTTGCTG
$P2Y_1$	Forward: CGCACACAGGTACAGTGGCGT Reverse: TTCCGAGTCCCAGTGCCAGAGT
$P2Y_2$	Forward: GTGCGGGGAACCCGGATCAC Reverse: AGCCGCCTGGCCATAAGCAC
$P2Y_6$	Forward: CCTTCGCTGCTGCCTACAA Reverse: TCTCTGCCTCTGCCACTTG
$P2Y_{10}$	Forward: ACCATTGCATGTTGTACCTGG Reverse: AGTGAAGCAGATAACGAAGACTG
$P2Y_{12}$	Forward: TCATCTATCTCAAGAACA Reverse: CGTACATATTAACATAGAAG
$P2Y_{13}$	Forward: CTGGAATCACTTGCTAAT Reverse: GTCACTAATCAATAGGAACT
ISG15	Forward: CAGGACGGTCTTACCCTTTCC Reverse: AGGCTCGCTGCAGTTCTGTAC
VSV	Forward: ACGGCGTACTTCCAGATGG Reverse: CTCGGTTCAAGATCCAGGT
NDV	Forward: TATACACCTCATCTCAGACAGGGTCAATCA Reverse: GCTCTCTTTAAGTCGGAGGATGTTGGC
HSV-1	Forward: CATCACCGACCCGGAGAGGGAC Reverse: GGGCCAGGCGCTTGTTGGTGTA
EPAC1	Forward: GCTCTCCCCTCCTGTCATCC Reverse: GTTCCCGCTGGTTGTCAATG
IFN-α	Forward: CGCAGGAGAAGGTGGATGCCCAG Reverse: CAGCACATTGGCAGAGGAAGACAGG
IFN-β	Forward: CAGCTCCAAGAAAGGACGAAC Reverse: GGCAGTGTAACTCTTCTGCAT

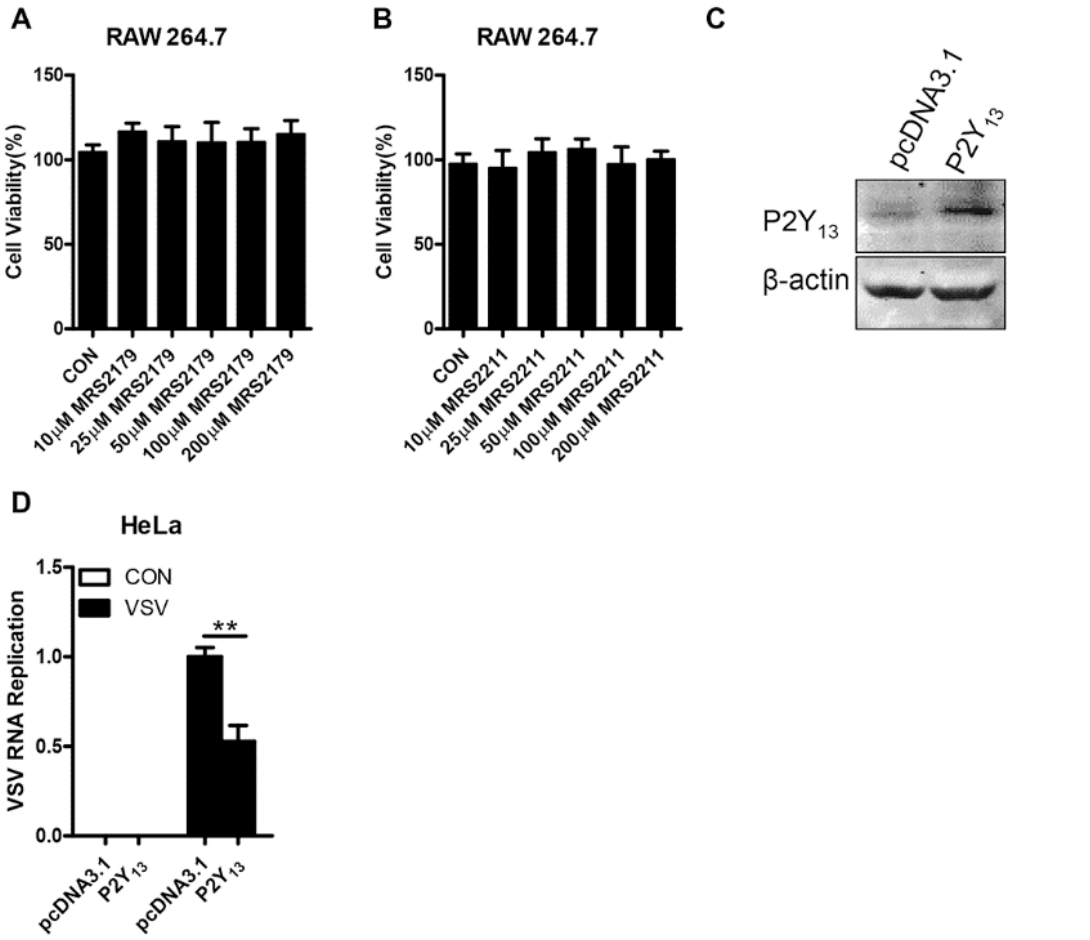


Supplementary Figure S1 ADP protects human cell lines against virus infection, related to Figure 2.

(A) HEK293T cells were infected with HSV-1 (MOI=0.01) for 24 h, and then the levels of ADP release were measured. (B) RAW264.7 and HEK293T cells were treated with various concentrations of ADP for 24 h, cell viability was detected by MTS assay. (C) Mice BMDMs were treated with various concentrations of ADP for 6 h and then infected with VSV (MOI=1)

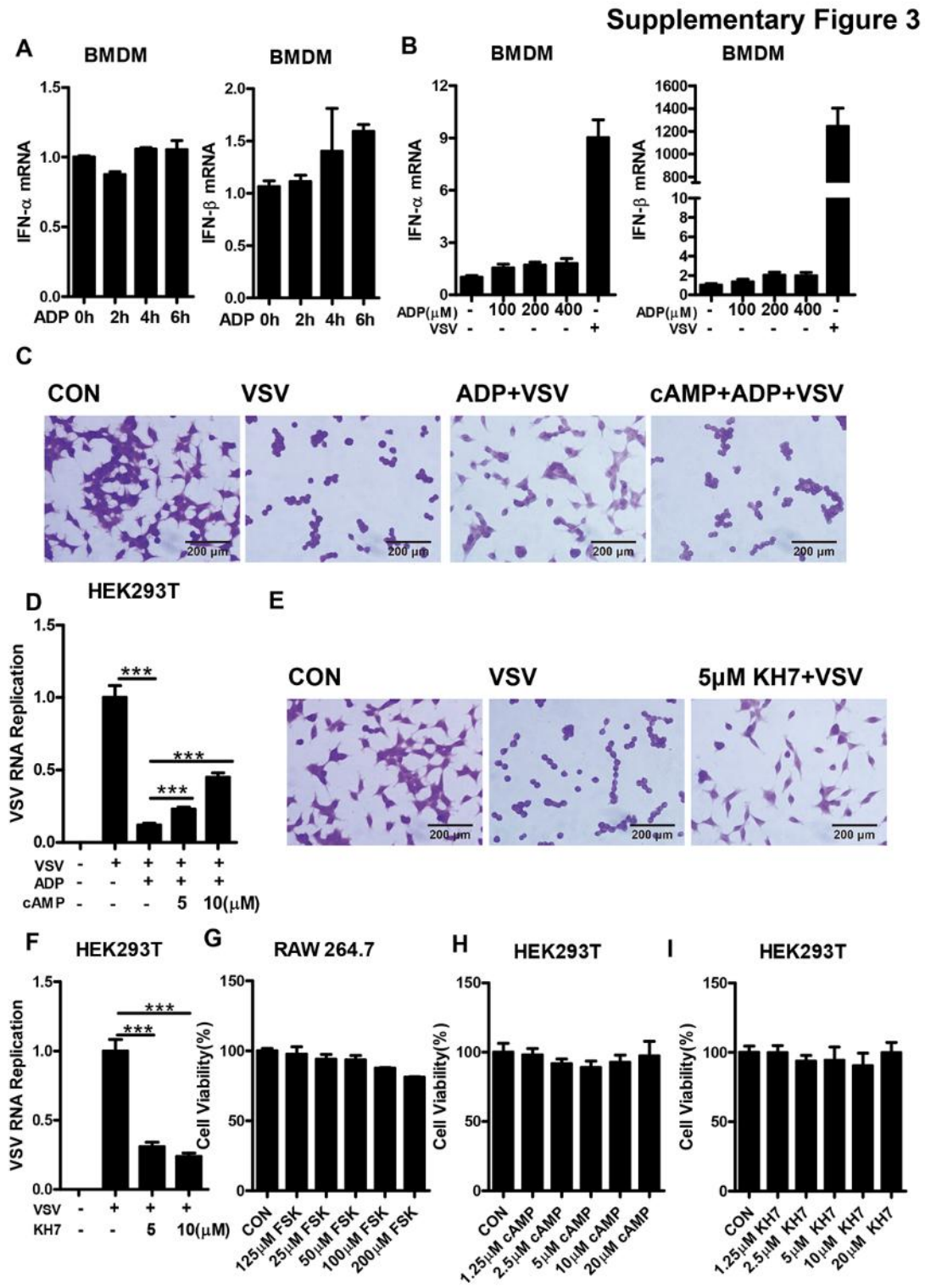
for 12 h, VSV RNA replicates were detected by Q-PCR. (D) HEK293T cells were pretreated with ADP (100 μM) for 6 h and then infected with VSV (MOI = 0.01) for 12 h. The cells were then fixed and stained by crystal violet, images were taken under microscopy. Scale bars = 200 μm. (E) HEK293T cells were treated with ADP (100 μM or 400 μM) for 6 h and then infected with HSV-1 (MOI = 0.01) for 12 h. The cells were then fixed and stained by crystal violet, images were taken under microscopy. Scale bars = 200 μm. (F) HEK293T cells and (G) HeLa cells were treated with ADP (100 μM or 400 μM) for 6 h and then infected with VSV-GFP (MOI=0.01) for 24 h. Cells containing GFP were analyzed by FACS. (H) HEK293T cells and (I) HeLa cells were treated as in (F) and then infected with MLV-GFP (as indicated MOI) for 24 h. Cells containing GFP were analyzed by FACS. (J) RAW264.7 cells were treated with ADP or ADP-β-s (100 μM) for 6 h and then infected with VSV (MOI = 0.01) for 12 h, VSV RNA replicates were detected by Q-PCR. Data are shown as mean ±SD. *p<0.05; **p<0.01; ***p<0.001; ns, not significant.

Supplementary Figure 2



Supplementary Figure S2 Overexpression of $P2Y_{13}$ suppresses VSV replication, related to Figure 3.

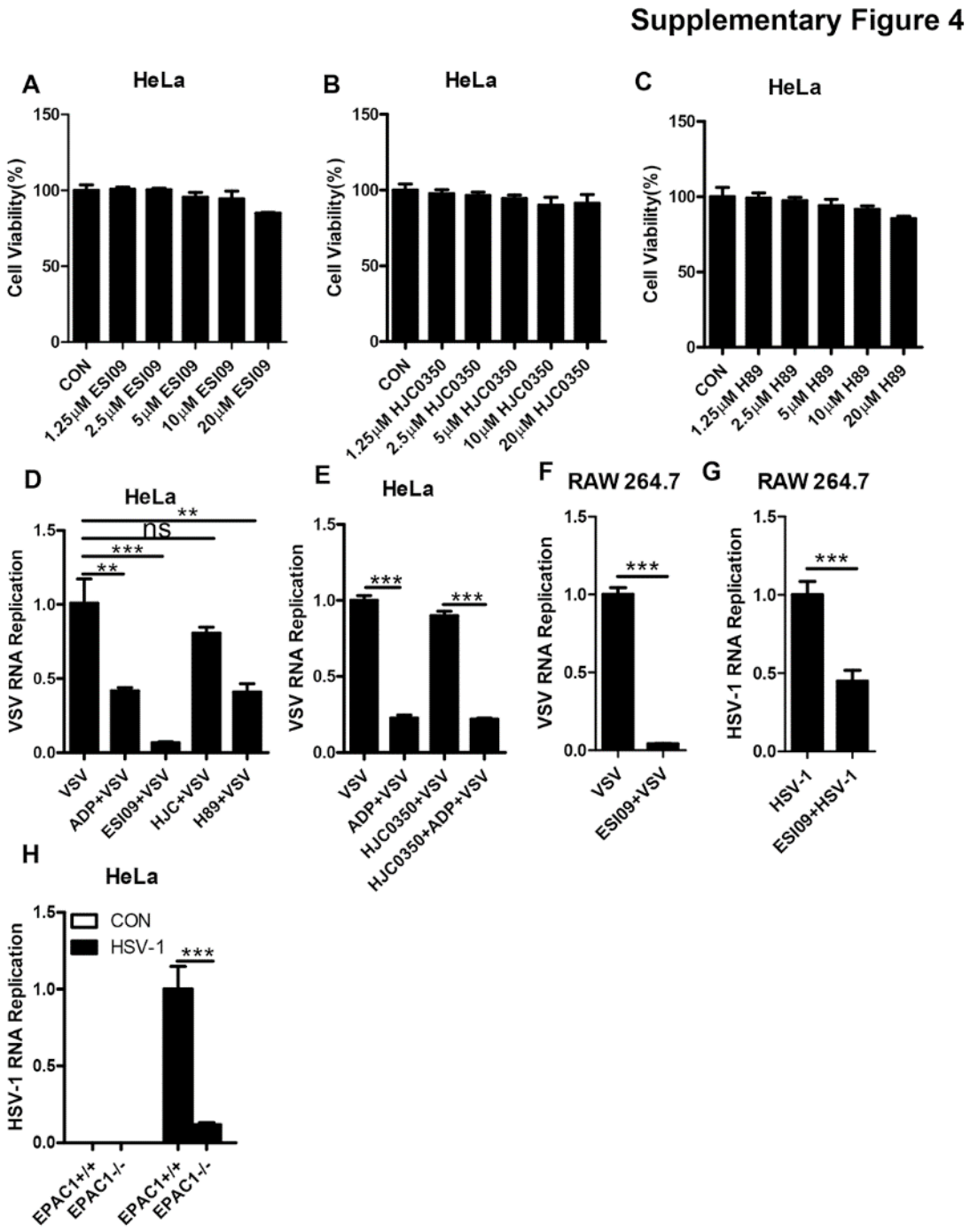
(A and B) RAW264.7 cells were treated with various concentrations of MRS 2179 or MRS 2211 for 24 h, cell viability was detected by MTS assay. (C) HeLa cells were transfected with pcDNA3.1 or $P2Y_{13}$ plasmid (1μg for 12-well plates) for 48 h, $P2Y_{13}$ expression levels were detected by Western blotting. (D) HeLa cells were transfected with pcDNA3.1 or $P2Y_{13}$ plasmid (1μg for 12-well plates) for 48 h and then infected with VSV (NOI=0.01) for 12 h, VSV RNA replicates were detected by Q-PCR. Data are shown as mean ±SD. $^{**}p<0.01$.



Supplementary Figure S3 Data related to Figure 5.

(A) Mice BMDMs were stimulated with ADP (100 μM) for the indicated time, IFN-α and IFN-β mRNA expression levels were measured by Q-PCR. (B) Mice BMDMs were stimulated with various concentrations of ADP or infected with VSV (MOI=1) for 6 h, IFN-α and IFN-β mRNA expression were measured by Q-PCR. (C) HEK293T cells were pretreated

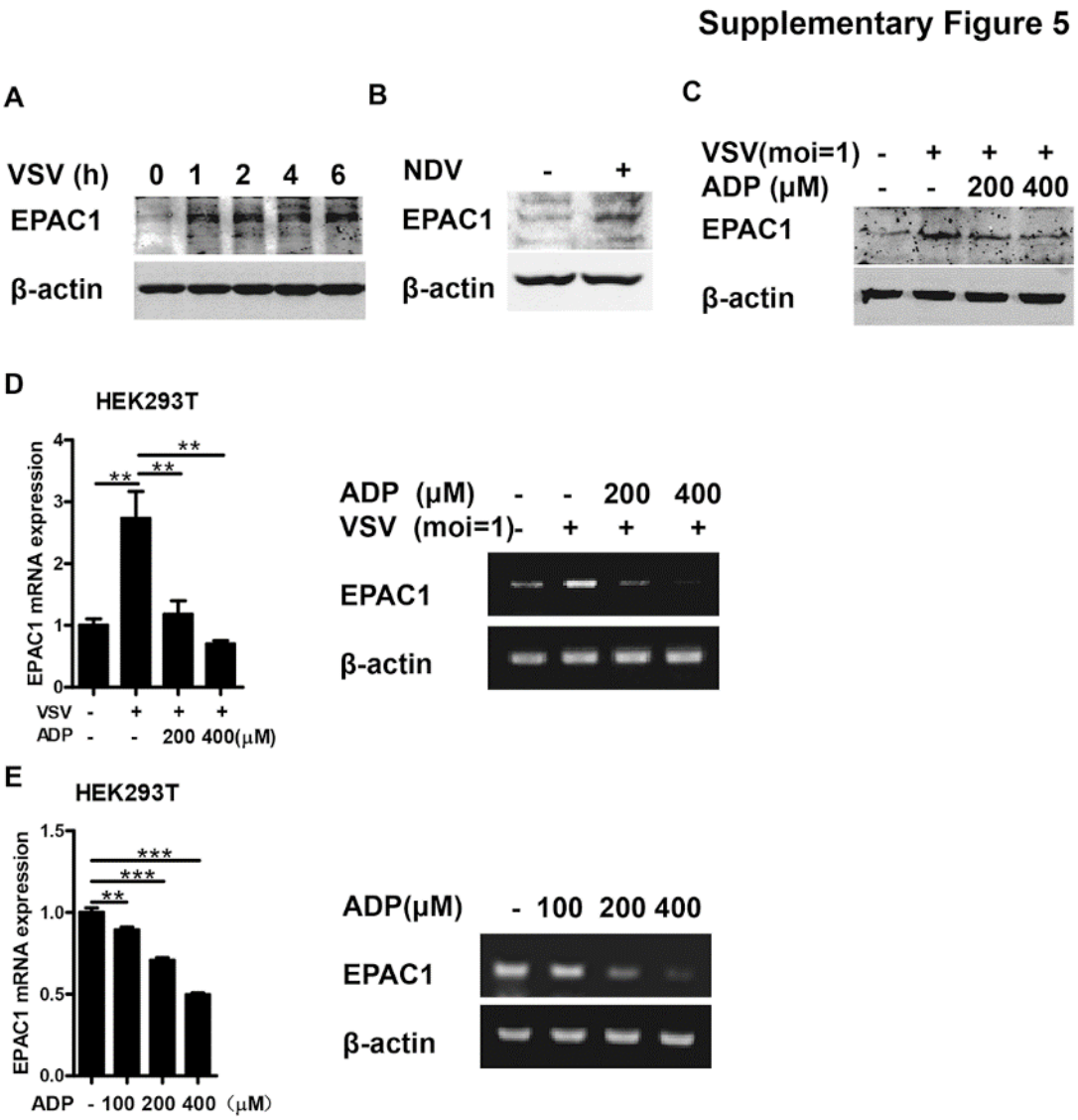
with cAMP (10 μM) for 30 min before being treated with ADP (100 μM) and then infected with VSV (MOI=0.01) for 12 h. The cells were then fixed and stained by crystal violet, images were taken under microscopy. Scale bars = 200 μm. (D) HEK293T cells were pretreated or not with cAMP (5 or 10μM) for 30 min before being exposed to ADP (100 μM) for 6 h. The cells were then infected with VSV (MOI = 0.01) for 12 h, VSV RNA replicates were measured by Q-PCR. (E) HEK293T cells were treated with KH7 (5 μM) for 30 min and then infected with VSV (MOI = 0.01) for 12 h. The cells were then fixed and stained by crystal violet, images were taken under microscopy. Scale bars = 200 μm. (F) HEK293T cells were treated with KH7 (5 or 10μM) for 30 min and then infected with VSV (MOI = 0.01) for 12 h, VSV RNA replicates were detected by Q-PCR. (G) RAW264.7 cells were treated with various concentrations of forskolin for 24 h, cell viability was detected by MTS assay. (H and I) HEK293T cells were treated with various concentrations of cAMP or KH7 for 24 h, cell viability was detected by MTS assay. Data are shown as mean ±SD. ***$p<0.001$.



Supplementary Figure S4 Data related to Figure 6.

(A-C) HeLa cells were treated with various concentrations of ESI-09, HJC0350 or H89 for 24 h, cell viability was detected by MTS assay. (D) HeLa cells were treated with ESI-09 (10 μM), HJC0350 (10 μM), H89 (10 μM) or ADP (100 μM) for 6 h and then infected with VSV (MOI = 0.01) for 12 h, VSV RNA replicates were detected by Q-PCR. (E) HeLa cells were pretreated or not with HJC0350 (10 μM) for 1 h before being treated with ADP (100 μM) for 6 h. The cells were then infected with VSV (MOI = 0.01) for 12 h, VSV RNA replicates were

detected by Q-PCR. (F) RAW264.7 cells were treated with ESI-09 (10 μM) for 6 h and then infected with VSV (MOI = 0.01) for 12 h, VSV RNA replicates were detected by Q-PCR. (G) RAW264.7 cells were treated with ESI-09 (10 μM) for 6 h and then infected with HSV-1 (MOI = 0.01) for 16 h, HSV-1 RNA replicates were detected by Q-PCR. (H) $EPAC1^{+/+}$ and $EPAC1^{-/-}$ HeLa cells were infected with HSV-1 (MOI = 0.01) for 16 h, HSV-1 RNA replicates were detected by Q-PCR. Data are shown as mean ±SD. $^{**}p<0.01$; $^{***}p<0.001$; ns, not significant.



Supplementary Figure S5 Data related to Figure 7.

(A) Mice BMDMs were infected with VSV (MOI = 5) for the indicated time. EPAC1 expression levels were detected by Western blotting. (B) HeLa cells were infected with NDV (MOI=0.01) for 24 h and EPAC1 expression levels were detected by Western blotting. (C) RAW264.7 cells were treated with ADP (200 μM or 400 μM) for 6 h and then infected with VSV (MOI = 1) for 6 h, EPAC1 expression levels were detected by Western blotting. (D) HEK293T cells were treated with different concentrations of ADP for 1 h and then infected with VSV (MOI = 0.01) for 2 h, EPAC1 expression was measured by Q-PCR and analyzed by RT-PCR. (E) HEK293T cells were treated with different concentrations of ADP for 2 h, EPAC1 expression was measured by Q-PCR and analyzed by RT-PCR. Data are shown as mean ±SD. ** $p<0.01$; *** $p<0.001$.