

SUPPLEMENTAL MATERIAL

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Table S1. Mass spectrometry analysis of binding partner of exogenous human USP21 in HeLa infected with HSV-1

Protein	Identified peptide
Mitogen-activated protein kinase 14	YQNLSVPGSGAYGSVcAAFDTK
Mitogen-activated protein kinase 14	LSRPFQSIHAK
Mitogen-activated protein kinase 14	MNFANVFIGANPLAVDLLEK
Mitogen-activated protein kinase 14	HENVIGLLDVFTPAR
Mitogen-activated protein kinase 14	LTDDHVQFLIYQILR
Mitogen-activated protein kinase 14	DLKPSNLAVNEDcELK
Stimulator of IFN genes protein	LIAYQEPADDSSFSLSQEVLR
Stimulator of IFN genes protein	TLEDILADAPESQNNcR
Stimulator of IFN genes protein	QEEKEEVTVGS�K
Stimulator of IFN genes protein	VYSNSIYELLENGQR

Table S2. Mass spectrometry analysis of serine-phosphorylated residues of exogenous human USP21 in HeLa infected with HSV-1

Site	Identified peptide	Modification
S93	ADHGVPLPGsPPPTVALPLPSR	S10(Phospho)
S335	RAPPILANGPVPsPPRR	S13(Phospho)
	APPILANGPVPsPPR	S12(Phospho)
	RAPPILANGPVPsPPR	S13(Phospho)
	APPILANGPVPsPPRR	S12(Phospho)
S538	CQTGWVHYNDSRVsPVSENQVASSEGYVLFYQLMQEPPR	S14(Phospho)

Table S3. Inhibitor library information

Gel	No.	Name or activity	M.W.	Con. (mM)	Purity by HPLC (%)	PubChem Compound ID#	p-USP21 Intensity
Gel 1 (top)	1	DMSO					+++
Gel 1 (top)	2	Akt Inhibitor V,Triciribine	320.3	10	99.16	290486	+++
Gel 1 (top)	3	Aurora Kinase Inhibitor II	400.4	10	98.70	6610278	++
Gel 1 (top)	4	DNA-PK Inhibitor II	281.3	10	99.70	9860529	++
Gel 1 (top)	5	EGFR Inhibitor	413.4	10	99.34	9549299	+
Gel 1 (top)	6	JAK Inhibitor I	309.3	10	98.51	5494425	++
Gel 1 (top)	7	JAK3 Inhibitor IV	367.9	10	97.86	176406	++
Gel 1 (top)	8	Rapamycin	914.2	10	95.71	16760631	++
Gel 1 (top)	9	TGF- $\beta$ RI Kinase Inhibitor	272.3	10	100.00	447966	++
Gel 1 (top)	10	VEGFR Tyrosine Kinase Inhibitor IV	472.9	10	97.75	9549295	++
Gel 1 (top)	11	SB202190 p38 inhibitor	331.3	10	98.00	5353940	-
Gel 2 (bottom)	12	DMSO					+++
Gel 2 (bottom)	13	ATM Kinase Inhibitor	395.5	10	99.00	5278396	+++
Gel 2 (bottom)	14	Cdk1 Inhibitor	294.7	10	100.00	5472558	+++
Gel 2 (bottom)	15	Casein Kinase I Inhibitor, D4476	398.4	10	99.90	6419753	+++
Gel 2 (bottom)	16	ERK Inhibitor III	318.3	10	97.90	5339183	+++
Gel 2 (bottom)	17	ERK Inhibitor II, FR180204	327.3	10	99.00	11493598	+++
Gel 2 (bottom)	18	GSK-3 $\beta$ Inhibitor I	222.3	10	98.60	4124851	+++
Gel 2 (bottom)	19	IC261	311.3	10	95.90	3674	+++
Gel 2 (bottom)	20	JNK Inhibitor II	220.2	10	99.00	8515	+++
Gel 2 (bottom)	21	JNK Inhibitor, Negative Control	234.2	10	99.90	11665831	+++
Gel 2 (bottom)	22	MEK Inhibitor I	374.5	10	96.80	9951490	+++

Table S4. **Primer for *Usp21* mice genotype identification**

Primers	
Primer for <i>Usp21</i> genotype identification	
<i>Usp21-1</i>	5'-GGTGAGGACTTGACAGCACA-3'
<i>Usp21-2</i>	5'-CCTAAGGACCCAAGGAAGAA-3'
<i>Usp21-3</i>	5'-AACTACAAGGGGATCCCAAG-3'
Primer for <i>Lyz2</i> genotype identification	
<i>Lyz2-1</i>	5'-CCCAGAAATGCCAGATTACG-3'
<i>Lyz2-2</i>	5'-CTGGGCTGCCAGAATTCTC-3'
<i>Lyz2-3</i>	5'-TTACAGTCGGCCAGGCTGAC-3'

Table S5. **qPCR primers**

Type	Primer
<i>Gapdh: sense</i>	5'-GTCGTGGAGTCTACTGGTGTG-3'
<i>Gapdh: antisense</i>	5'-GAGCCCTCCACAATGCCAAA-3'
<i>Ifnb: sense</i>	5'-TCCGAGCAGAGATCTTCAGGAA-3'
<i>Ifnb: antisense</i>	5'-TGCAACCACCACTCATTCTGAG-3'
<i>Ifna4: sense</i>	5'-CCTGTGTGATGCAGGAACC-3'
<i>Ifna4: antisense</i>	5'-TCACCTCCCAGGCACAGA-3'
<i>Isg15: sense</i>	5'-TGGCCTGGGACCTAAAGGTGAAGA-3'
<i>Isg15: antisense</i>	5'-TGCACTGGGCTTTAGGCCATACT-3'
<i>Tnfa: sense</i>	5'-GACCCCTCACACTCAGATCAT-3'
<i>Tnfa: antisense</i>	5'-TTGAAGAGAACCTGGGAGTA-3'
<i>Usp21: sense</i>	5'-TGCGTCCAATGGGGATTGC-3'
<i>Usp21: antisense</i>	5'-GGCTCTGTCCGTATGCTGA-3'
<i>GAPDH: sense</i>	5'-TCTCCTCTGTGCTCTTGC-3'
<i>GAPDH: antisense</i>	5'-TCTGACTTCAACAGCGACAC-3'
<i>USP21: sense</i>	5'-CGAATCCTCGTGCTCCATC-3'
<i>USP21: antisense</i>	5'-GCTCCTGCATCAGTTGGTAG-3'
<i>IFN<math>\beta</math>: sense</i>	5'-CACGACAGCTCTTCCATGA-3'
<i>IFN<math>\beta</math>: antisense</i>	5'-AGCCAGTGCTCGATGAATCT-3'
<i>VSV: sense</i>	5'-ACGGCGTACTTCCAGATGG-3'
<i>VSV: antisense</i>	5'-CTCGGTTCAAGATCCAGGT-3'