Figure S1: TEpi cell death during intracellular infection with JRS4 or 5448 GAS strains.

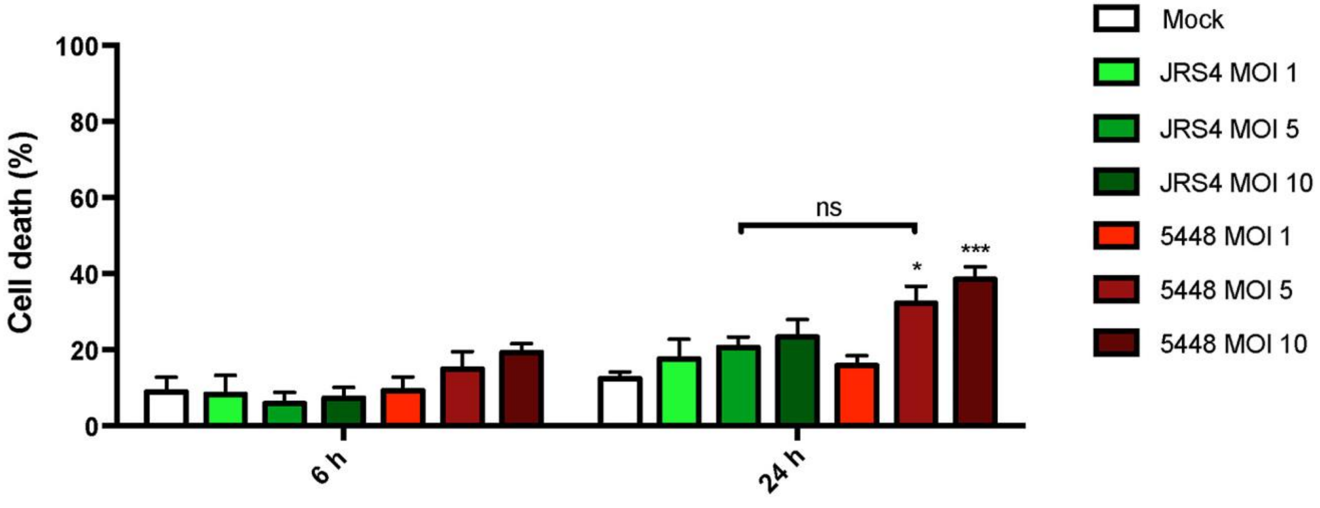
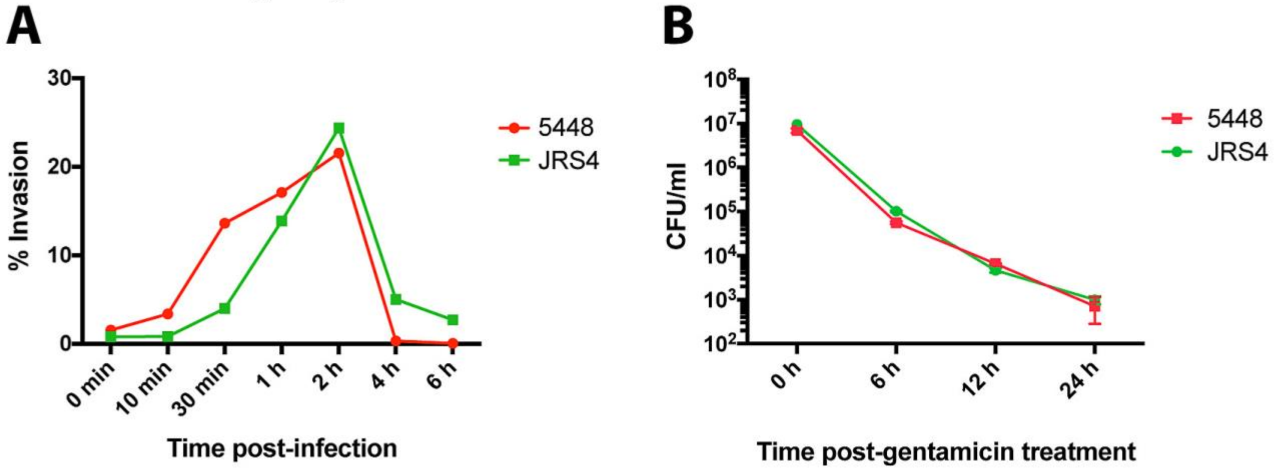


Figure S2: Invasion rate and intracellular survival of JRS4 and 5448 GAS strains during TEpi cell infection.



```
             10        20        30        40        50        60
              |         |         |         |         |         |
5448 MEKKQRFSLRKYKSGTFSVLIGSVFLVM-TTTVAADELSTMSEPTITNHAQQQAQHLTNT
JRS4 MEKKQRFSLRKYKSGTFSVLIGSVFLMMMTTTVAADELTTTSEPTITNHAQQQAQHLTNT
     **************************:* *********:* *******************

             70        80        90       100       110       120
              |         |         |         |         |         |
     ELSSAESKSQDTSQITLKTNREKEQSQDLVSEPTTTELADTDAASMANTGSDATQKSASL
     ELSSAESKPQDTSQITPKTNREKEQSQDLVSEPTTTELADTDAASMANTGPDATQKSASL
     ********.******* *********************************.*********

            130       140       150       160       170       180
              |         |         |         |         |         |
     PPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
     PPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
     ************************************************************

            190       200       210       220       230       240
              |         |         |         |         |         |
     RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHK
     RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHK
     ************************************************************

            250       260       270       280       290       300
              |         |         |         |         |         |
     IYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGE
     IYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGE
     ************************************************************

            310       320       330       340       350       360
              |         |         |         |         |         |
     RFLGIAPEAQVMFMRVFANDIMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSK
     RFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSK
     ********************:***************************************

            370       380       390       400       410       420
              |         |         |         |         |         |
     PLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINS
     PLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINS
     ************************************************************

            430       440       450       460       470       480
              |         |         |         |         |         |
     KWVIQRLMTVKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKESTDAGYNA
     KWVIQRLMTVKELENRADLNHGKAIYSESVDFKNIKDSLGYDKSHQFAYVKESTDAGYNA
     *********************************:**************************

            490       500       510       520       530       540
              |         |         |         |         |         |
     QDVKGKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTANGMGIPSAF
     QDVKGKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTSNGMGIPSAF
     **************************************************:*********

            550       560       570       580       590       600
              |         |         |         |         |         |
     ISHEFGKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGG
     ISHEFGKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGG
     ************************************************************

            610       620       630       640       650       660
              |         |         |         |         |         |
     DIYSTYNDNHYGSQTGTSMASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQ
     DIYSTYNDNHYGSQTGTSMASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQ
     ************************************************************
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           670       680       690       700       710       720
             |         |         |         |         |         |
5448 IHVNPETKTTTSPRQQGAGLLNIDGAVTSGLYVTGKDNYGSISLGNITDTMTFDVTVHNL
JRS4 IHVNPETKTTTSPRQQGAGLLNIDGAVTSGLYVTGKDNYGSISLGNVTDTMTFDVTVHNL
     **********************************************:*************

           730       740       750       760       770       780
             |         |         |         |         |         |
     SNKDKTLRYDTELLTDHVDPQKGRFTLTSHSLKTYQGGEVTVPANGKVTVRVTMDVSQFT
     SNKAKTLRYDTELLTDHVDPQKGRFTLTSRSLKTYQGGEVTVPANGKVTVRVTMDVSQFT
     *** *************************:******************************

           790       800       810       820       830       840
             |         |         |         |         |         |
     KELTKQMPNGYYLEGFVRFRDSQDDQLNRVNIPFVGFKGQFENLAVAEESIYRLKSQGKT
     KELTKQMPNGYYLEGFVRFRDSQDDQLNRVNIPFVGFKGQFENLAVAEESIYRLKSQGKT
     ************************************************************

           850       860       870       880       890       900
             |         |         |         |         |         |
     GFYFDESGPKDDIYVGKHFTGLVTLGSETNVSTKTISDNGLHTLGTFKNADGKFILEKNA
     GFYFDESGPKDDIYVGKHFTGLVTLGSETNVSTKTISDNGLHTLGTFKNADGKFILEKNA
     ************************************************************

           910       920       930       940       950       960
             |         |         |         |         |         |
     QGNPVLAISPNGDNNQDFAAFKGVFLRKYQGLKASVYHASDKEHKNPLWVSPESFKGDKN
     QGNPVLAISPNGDNNQDFAAFKGVFLRKYQGLKASVYHASDKEHKNPLWVSPESFKGDKN
     ************************************************************

           970       980       990      1000      1010      1020
             |         |         |         |         |         |
     FNSDIRFAKSTTLLGTAFSGKSLTGAELPDGHYHYVVSYYPDVVGAKRQEMTFDMILDRQ
     FNSDIRFAKSTTLLGTAFSGKSLTGAELPDGYYHYVVSYYPDVVGAKRQEMTFDMILDRQ
     *******************************:****************************

          1030      1040      1050      1060      1070      1080
             |         |         |         |         |         |
     KPVLSQATFDPETNRFKPEPLKDRGLAGVRKDSAFYLERKDNKPYTVTINDSYKYVSVED
     KPVLSQATFDPETNRFKPEPLKDRGLAGVRKDSVFYLERKDNKPYTVTINDSYKYVSVED
     *********************************.**************************

          1090      1100      1110      1120      1130      1140
             |         |         |         |         |         |
     NKTFVERQADGSFILPLDKAKLGDFYYMVEDFAGNVAIAKLGDHLPQTLGKTPIKLKLTD
     NKTFVERQADGSFILPLDKAKLGDFYYMVEDFAGNVAIAKLGDHLPQTLGKTPIKLKLTD
     ************************************************************

          1150      1160      1170      1180      1190      1200
             |         |         |         |         |         |
     GNYQTKETLKDNLEMTQSDTGLVTNQAQLAVVHRNQPQSQLTKMNQDFFISPNEDGNKDF
     GNYQTKETLKDNLEMTQSDTGLVTNQAQLAVVHRNQPQSQLTKMNQDFFISPNEDGNKDF
     ************************************************************

          1210      1220      1230      1240      1250      1260
             |         |         |         |         |         |
     VAFKGLKNNVYNDLTVNVYAKDDHQKQTPIWSSQAGASVSAIESTAWYGITARGSKVMPG
     VAFKGLKNNVYNDLTVNVYAKDDHQKQTPIWSSQAGASASAIESTAWYGITARGSKVMPG
     **************************************.*********************

          1270      1280      1290      1300      1310      1320
             |         |         |         |         |         |
     DYQYVVTYRDEHGKEHQKQYTISVNDKKPMITQGRFDTINGVDHFTPDKTKALGSSGIVR
     DYQYVVTYRDEHGKEHQKQYTISVNDKKPMITQGRFDTINGVDHFTPDKTKALGSSGIVR
     ************************************************************
```

```
           1330      1340      1350      1360      1370      1380
              |         |         |         |         |         |
5448 EEVFYLAKKNGRKFDVTEGKDGITVSDNKVYIPKNPDGSYTISKRDGVTLSDYYYLVEDR
JRS4 EEVFYLAKKNGRKFDVTEGKDGITVSDNKVYIPKNPDGSYTISKRDGVTLSDYYYLVEDR
     ************************************************************

           1390      1400      1410      1420      1430      1440
              |         |         |         |         |         |
     AGNVSFATLRDLKAVGKDKAVVNFGLDLPVPEDKQIVNFTYLVRDADGKPIENLEYYNNS
     AGNVSFATLRDLKAVGKDKAVVNFGLDLPVPEDKQIVNFTYLVRDADGKPIENLEYYNNS
     ************************************************************

           1450      1460      1470      1480      1490      1500
              |         |         |         |         |         |
     GNSLILPYGKYTVELLTYDTNAAKLESDKIVSFTLSADNNFQQVTFKITMLATSQITAHF
     GNSLILPYGKYTVELLTYDTNAAKLESDKIVSFTLSADNNFQQITFKMTMLATSQITAHF
     *******************************************:***:************

           1510      1520      1530      1540      1550      1560
              |         |         |         |         |         |
     DHLLPEGSRVSLKTAQDQLIPLEQSLYVPKAYGKTVQEGTYEVVVSLPKGYRIEGNTKVN
     DHLLPEGSRVSLKTAQGQLIPLEQSLYVPKAYGKTVQEGTYEVVVSLPKGYRIEGNTKVN
     ****************.*******************************************

           1570      1580      1590      1600      1610      1620
              |         |         |         |         |         |
     TLPNEVHELSLRLVKVGDASDSTGDHKVMSKNNSQALTASATPTKSTTSATAKALPSTGE
     TLPNEVHELSLRLVKVGDASDSTGDHKVMSKNNSQALTASATPTKTTTSATAKALPSAGE
     *********************************************:***********:**

           1630      1640
              |         |
     KMGLKLRIVGLVLLGLTCVFSRKKSTKD
     KMGLKLRIVGLVLLGLTCVFSRKKSTKD
     ****************************
```

Figure S4: RNAseq transcriptome network and pathway enrichment of 5448 GAS-intracellularly infected primary tonsil epithelial cells in comparison to JRS4-infected cells.

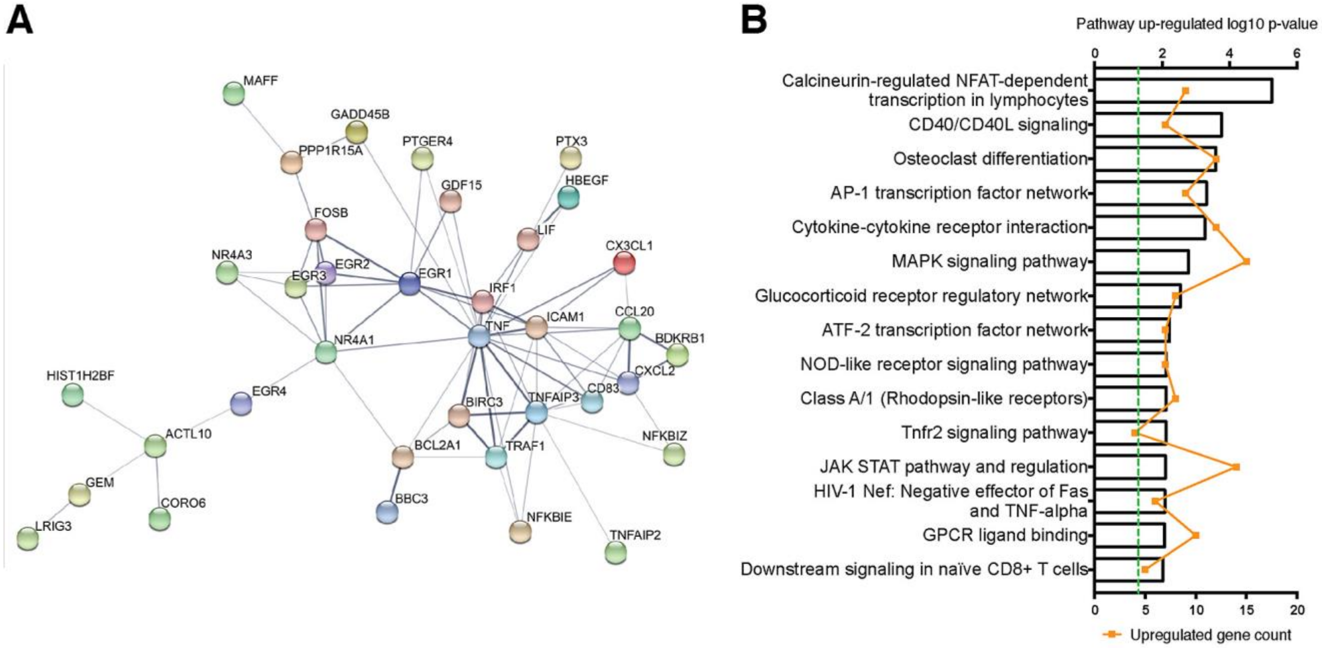

Table S1. Metadata for transcriptome interaction network and pathway analysis of 5448 intracelluarly infected TEpi cells in comparison to mock TEpi cells.

Gene symbol	Full name	Log2FC gene expression in comparison to Mock cells	Adjusted P-value	Protein-protein interaction data type from Stringdb.com	Upregulated pathways from Innatedb.com
FOSB	FBJ murine osteosarcoma viral oncogene homolog B	5.412	7.89E-06	experimentally determined, textmining	AP-1 transcription factor network, Osteoclast differentiation
TNF	tumor necrosis factor	5.228	7.66E-06	coexpression, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Cytokine-cytokine receptor interaction, Osteoclast differentiation, GPCR signaling, IL23-mediated signaling events, MAPK signaling pathway, Signal transduction through il1r, NOD-like receptor signaling pathway, TWEAK, amb2 Integrin signaling, Downstream signaling in naïve CD8+ T cells, Toll-like receptor signaling pathway, Hematopoietic cell lineage, Hepatitis C, Keratinocyte differentiation, Leishmaniasis, HIV-1 Nef: Negative effector of Fas and TNF-alpha, T cell receptor signaling pathway, TNFR1 signaling pathway, TNF receptor signaling pathway
CXCL2	chemokine (C-X-C motif) ligand 2	4.717	3.18E-05	coexpression, curated databases, protein homology, textmining	Cytokine-cytokine receptor interaction, GPCR ligand binding, Class A/1 (Rhodopsin-like receptors), NOD-like receptor signaling pathway, Chemokine receptors bind chemokines, Signaling by GPCR, Peptide ligand-binding receptors, GPCR downstream signaling, G alpha (i) signalling events
IL8	interleukin 8	4.657	2.17E-05	coexpression, curated databases, protein homology, textmining	AP-1 transcription factor network, ATF-2 transcription factor network, Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Cytokine-cytokine receptor interaction, Validated transcriptional targets of AP1 family members Fra1 and Fra2, GPCR signaling, GPCR ligand binding, Class A/1 (Rhodopsin-like receptors), NOD-like receptor signaling pathway, Chemokine receptors bind chemokines, Glucocorticoid receptor regulatory network, Signaling by GPCR, Toll-like receptor signaling pathway, Senescence-Associated Secretory Phenotype (SASP), Peptide ligand-binding receptors, Hepatitis C, GPCR downstream signaling, G alpha (i) signalling events
ATF3	activating transcription factor 3	4.384	7.98E-05	experimentally determined, coexpression, protein homology, textmining	AP-1 transcription factor network, ATF-2 transcription factor network, Direct p53 effectors
EGR2	early growth response 2	4.337	1.07E-05	experimentally determined, coexpression, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes

PPP1R15A	protein phosphatase 1, regulatory subunit 15A	4.057	6.32E-07	coexpression, textmining	None
EGR4	early growth response 4	3.975	1.33E-04	experimentally determined, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Downstream signaling in naïve CD8+ T cells
TNFAIP3	tumor necrosis factor, alpha-induced protein 3	3.969	9.07E-06	experimentally determined, coexpression, textmining	CD40/CD40L signaling, NOD-like receptor signaling pathway, Tnfr2 signaling pathway, RIG-I/MDA5 mediated induction of IFN-alpha/beta pathways, TNF receptor signaling pathway
TRAF1	TNF receptor-associated factor 1	3.928	6.14E-05	experimentally determined, curated databases, coexpression, textmining	CD40/CD40L signaling, TWEAK, Tnfr2 signaling pathway, RANKL, Keratinocyte differentiation, HIV-1 Nef: Negative effector of Fas and TNF-alpha, TNF receptor signaling pathway
CCL20	chemokine (C-C motif) ligand 20	3.897	2.41E-05	coexpression, curated databases, textmining	Cytokine-cytokine receptor interaction, GPCR ligand binding, Class A/1 (Rhodopsin-like receptors), NOD-like receptor signaling pathway, Chemokine receptors bind chemokines, Signaling by GPCR, Peptide ligand-binding receptors, GPCR downstream signaling, G
LIF	leukemia inhibitory factor	3.869	1.34E-04	curated databases, textmining	Cytokine-cytokine receptor interaction, Validated transcriptional targets of AP1 family members Fra1 and Fra2, GPCR signaling, Direct p53 effectors, Jak-STAT signaling pathway
HBEGF	heparin-binding EGF-like growth factor	3.869	4.81E-06	curated databases, textmining	GPCR signaling, Signaling by GPCR, ErbB receptor signaling network
IRF1	interferon regulatory factor 1	3.811	7.98E-05	experimentally determined, coexpression, curated databases, textmining	Glucocorticoid receptor regulatory network, Cytokine Signaling in Immune system, IL6-mediated signaling events, Interferon alpha/beta signaling, Hepatitis C, RIG-I/MDA5 mediated induction of IFN-alpha/beta pathways
EGR1	early growth response 1	3.811	1.23E-03	experimentally determined, coexpression, curated databases, textmining	AP-1 transcription factor network, Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Glucocorticoid receptor regulatory network, Cytokine Signaling in Immune system, Downstream signaling in naïve CD8+ T cells, Interferon alpha/beta signaling, Oncostatin_M

IL6	interleukin 6 (interferon, beta 2)	3.739	5.25E-04	coexpression, curated databases, textmining	AP-1 transcription factor network, ATF-2 transcription factor network, Cytokine-cytokine receptor interaction, Validated transcriptional targets of AP1 family members Fra1 and Fra2, GPCR signaling, IL23-mediated signaling events, Signal transduction through il1r, NOD-like receptor signaling pathway, Activated TLR4 signalling, Toll Like Receptor 4 (TLR4) Cascade, Toll-Like Receptors Cascades, Jak-STAT signaling pathway, MyD88 dependent cascade initiated on endosome, Toll Like Receptor 7/8 (TLR7/8) Cascade, Glucocorticoid receptor regulatory network, Cytokine Signaling in Immune system, Signaling by GPCR, amb2 Integrin signaling, Signaling by Interleukins, Toll Like Receptor 9 (TLR9) Cascade, MyD88:Mal cascade initiated on plasma membrane, Toll Like Receptor 2 (TLR2) Cascade, Toll Like Receptor TLR1:TLR2 Cascade, Toll Like Receptor TLR6:TLR2 Cascade, IL6-mediated signaling events, Toll-like receptor signaling pathway, MyD88 cascade initiated on plasma membrane, TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation, Toll Like Receptor 10 (TLR10) Cascade, Toll Like Receptor 5 (TLR5) Cascade, Hematopoietic cell lineage, MyD88-independent cascade, TRIF-mediated TLR3/TLR4 signaling, Toll Like Receptor 3 (TLR3) Cascade, Senescence-Associated Secretory Phenotype (SASP)
BIRC3	baculoviral IAP repeat containing 3	3.688	3.20E-05	experimentally determined, coexpression, curated databases, textmining	CD40/CD40L signaling, NOD-like receptor signaling pathway, Activated TLR4 signalling, Toll Like Receptor 4 (TLR4) Cascade, Toll-Like Receptors Cascades, MyD88-independent cascade, TRIF-mediated TLR3/TLR4 signaling, Toll Like Receptor 3 (TLR3) Cascade, Keratinocyte differentiation, HIV-1 Nef: Negative effector of Fas and TNF-alpha, TNF receptor signaling pathway
NR4A1	nuclear receptor subfamily 4, group A, member 1	3.674	1.58E-04	experimentally determined, coexpression, textmining	MAPK signaling pathway, Glucocorticoid receptor regulatory network
CD83	CD83 molecule	3.665	6.14E-05	coexpression, textmining	None
MAFF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	3.605	9.07E-06	experimentally determined, coexpression, textmining	Oxidative stress induced gene expression via nrf2
PTGS2	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	3.471	4.77E-04	coexpression, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Calcium signaling in the CD4+ TCR pathway, Leishmaniasis

NR4A3	nuclear receptor subfamily 4, group A, member 3	3.401	5.08E-04	experimentally determined, textmining	None
EGR3	early growth response 3	3.281	9.07E-06	experimentally determined, coexpression, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes
GADD45B	growth arrest and DNA-damage-inducible, beta	3.279	1.76E-05	experimentally determined, protein homology, textmining	MAPK signaling pathway, IL12-mediated signaling events
SOCS3	suppressor of cytokine signaling 3	3.276	9.07E-06	coexpression, curated databases, textmining	ATF-2 transcription factor network, Osteoclast differentiation, IL23-mediated signaling events, Jak-STAT signaling pathway, Cytokine Signaling in Immune system, Signaling by Interleukins, IL6-mediated signaling events, Interferon alpha/beta signaling, Hepatitis C, Oncostatin_M
DUSP5	dual specificity phosphatase 5	3.143	1.46E-05	experimentally determined, coexpression, textmining	ATF-2 transcription factor network, MAPK signaling pathway, Direct p53 effectors
CSF2	colony stimulating factor 2 (granulocyte-macrophage)	2.968	6.10E-04	coexpression, textmining	AP-1 transcription factor network, Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Cytokine-cytokine receptor interaction, GPCR signaling, Calcium signaling in the CD4+ TCR pathway, Jak-STAT signaling pathway, Glucocorticoid receptor regulatory network, Cytokine Signaling in Immune system, Signaling by GPCR, Signaling by Interleukins, Hematopoietic cell lineage, GPCR downstream signaling, T cell receptor signaling pathway
NFKBIE	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon	2.949	1.07E-05	experimentally determined, coexpression, textmining	T cell receptor signaling pathway, TNFR1 signaling pathway, B cell receptor signaling pathway
FOSL1	FOS-like antigen 1	2.891	3.82E-06	experimentally determined, coexpression, protein homology, curated databases, textmining	AP-1 transcription factor network, Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Osteoclast differentiation, Validated transcriptional targets of AP1 family members Fra1 and Fra2, Calcium signaling in the CD4+ TCR pathway, Downstream signaling in naïve CD8+ T cells,
PMAIP1	phorbol-12-myristate-13-acetate-induced protein 1	2.875	5.28E-06	experimentally determined, curated databases, textmining	Direct p53 effectors
EDN1	endothelin 1	2.833	7.07E-05	textmining	AP-1 transcription factor network, GPCR signaling, GPCR ligand binding, Class A/1 (Rhodopsin-like receptors), Signaling by GPCR, Peptide ligand-binding receptors, GPCR downstream signaling

BCL2A1	BCL2-related protein A1	2.825	5.55E-05	experimentally determined, curated databases, textmining	BCR signaling pathway
CXCL3	chemokine (C-X-C motif) ligand 3	2.785	8.39E-05	coexpression, curated databases, protein homology, textmining	Cytokine-cytokine receptor interaction, GPCR ligand binding, Class A/1 (Rhodopsin-like receptors), Chemokine receptors bind chemokines, Signaling by GPCR, Peptide ligand-binding receptors, GPCR downstream signaling, G alpha (i) signalling events
BBC3	BCL2 binding component 3	2.710	3.30E-04	experimentally determined, curated databases, textmining	Direct p53 effectors
SERPINB2	serpin peptidase inhibitor, clade B (ovalbumin), member 2	2.582	2.35E-04	curated databases, textmining	None
PLAUR	plasminogen activator, urokinase receptor	2.572	2.95E-06	coexpression, curated databases, textmining	Validated transcriptional targets of AP1 family members Fra1 and Fra2, amb2 Integrin signaling
ZFP36	zinc finger protein 36, C3H type, homolog (mouse)	2.524	2.25E-05	experimentally determined, coexpression, textmining	None
PRDM1	PR domain containing 1, with ZNF domain	2.449	1.67E-05	experimentally determined, textmining	Direct p53 effectors
PIM1	pim-1 oncogene	2.446	1.50E-04	experimentally determined, curated databases, textmining	Jak-STAT signaling pathway
PTX3	pentraxin 3, long	3.721	6.06E-04	coexpression, textmining	None
IL1RL1	interleukin 1 receptor-like 1	3.396	5.31E-04	textmining	None
IL24	interleukin 24	2.485	1.51E-04	textmining	Cytokine-cytokine receptor interaction, IL23-mediated signaling events

Table S2. Metadata for transcriptome interaction network and pathway analysis of JRS4 intracellularly infected TEpi cells in comparison to mock TEpi cells.

Gene symbol	Full name	Log2FC gene expression in comparison to Mock cells	Adjusted P-value	Protein-protein interaction data type from Stringdb.com	Upregulated pathways from Innatedb.com
ATF3	activating transcription factor 3	3.299	3.59E-03	experimentally determined, co-expression, protein homology, curated databases, textmining	AP-1 transcription factor network, ATF-2 transcription factor network, Direct p53 effectors
PTGS2	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	3.207	6.56E-03	curated databases, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Calcium signaling in the CD4+ TCR pathway, Leishmaniasis
IL8	interleukin 8	3.063	2.46E-03	co-expression, protein homology, curated databases, textmining	AP-1 transcription factor network, Cytokine-cytokine receptor interaction, ATF-2 transcription factor network, Calcineurin-regulated NFAT-dependent transcription in lymphocytes, GPCR signaling, Chemokine receptors bind chemokines, GPCR ligand binding, Signaling by GPCR, Class A/1 (Rhodopsin-like receptors), NOD-like receptor signaling pathway, Validated transcriptional targets of AP1 family members Fra1 and Fra2, Peptide ligand-binding receptors, Amoebiasis, GPCR downstream signaling, G alpha (i) signalling events, Nfkb activation by nontypeable hemophilus influenzae, Malaria
IL36G	interleukin 36, gamma	3.034	8.88E-05	co-expression, textmining	None
CXCL2	chemokine (C-X-C motif) ligand 2	2.897	4.46E-03	co-expression, protein homology, curated databases, textmining	Cytokine-cytokine receptor interaction, Chemokine receptors bind chemokines, GPCR ligand binding, Signaling by GPCR, Class A/1 (Rhodopsin-like receptors), NOD-like receptor signaling pathway, Peptide ligand-binding receptors, GPCR downstream signaling, G alpha (i) signalling events
IL6	interleukin 6 (interferon, beta 2)	2.847	1.82E-02	co-expresssion, curated databases, textmining	AP-1 transcription factor network, Cytokine-cytokine receptor interaction, ATF-2 transcription factor network, GPCR signaling, IL23-mediated signaling events, Signaling by GPCR, NOD-like receptor signaling pathway, Validated transcriptional targets of AP1 family members Fra1 and Fra2, Amoebiasis, Jak-STAT signaling pathway, Hematopoietic cell lineage, Signal transduction through il1r, Graft-versus-host disease, Malaria, Il-10 anti-inflammatory signaling pathway

CLDN4	claudin 4	2.743	5.47E-04	curated databases, protein homology, co-expression, textmining	None
TNF	tumor necrosis factor	2.606	3.08E-03	co-expression, textmining	Cytokine-cytokine receptor interaction, Calcineurin-regulated NFAT-dependent transcription in lymphocytes, GPCR signaling, IL23-mediated signaling events, NOD-like receptor signaling pathway, Amoebiasis, Hematopoietic cell lineage, Signal transduction through il1r, Graft-versus-host disease, Osteoclast differentiation, Nfkb activation by nontypeable hemophilus influenzae, Malaria, Il-10 anti-inflammatory signaling pathway, Leishmaniasis
SERPINB2	serpin peptidase inhibitor, clade B (ovalbumin), member 2	2.446	2.86E-03	curated databases, textmining	Amoebiasis
MMP3	matrix metallopeptidase 3 (stromelysin 1, progelatinase)	2.337	2.41E-02	textmining	Signaling by GPCR
CXCL3	chemokine (C-X-C motif) ligand 3	2.288	2.63E-03	co-expression, protein homology, curated databases, textmining	Cytokine-cytokine receptor interaction, Chemokine receptors bind chemokines, GPCR ligand binding, Signaling by GPCR, Class A/1 (Rhodopsin-like receptors), Peptide ligand-binding receptors, GPCR downstream signaling, G alpha (i) signalling events
IL1RL1	interleukin 1 receptor-like 1	2.282	3.35E-02	experimentally determined, textmining	None
TNFAIP3	tumor necrosis factor, alpha-induced protein 3	2.271	2.00E-03	experimentally determined, co-expression, textmining	NOD-like receptor signaling pathway
DUSP1	dual specificity phosphatase 1	2.141	1.48E-03	experimentally determined, co-expression, curated databases, textmining	AP-1 transcription factor network, ATF-2 transcription factor network, Direct p53 effectors, Nfkb activation by nontypeable hemophilus influenzae
DLX2	distal-less homeobox 2	2.136	2.63E-02	textmining	None
IL24	interleukin 24	2.006	4.50E-03	co-expression, textmining	Cytokine-cytokine receptor interaction, IL23-mediated signaling events, Jak-STAT signaling pathway
OCLN	occludin	2.004	2.86E-03	experimentally determined, textmining	None
PIM1	pim-1 oncogene	1.931	5.21E-03	experimentally determined, curated databases, textmining	Jak-STAT signaling pathway

EGR2	early growth response 2	1.930	1.08E-02	experimentally determined, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes
FOSB	FBJ murine osteosarcoma viral oncogene homolog B	1.929	2.03E-02	experimentally determined, curated databases, textmining	AP-1 transcription factor network, Osteoclast differentiation
PPP1R15A	protein phosphatase 1, regulatory subunit 15A	1.921	3.46E-04	co-expresssion, curated databases, textmining	None
DUSP5	dual specificity phosphatase 5	1.909	2.62E-03	experimentally determined, co-expression, textmining	ATF-2 transcription factor network, Direct p53 effectors
SOCS3	suppressor of cytokine signaling 3	1.830	2.62E-03	co-expresssion, curated databases, textmining	ATF-2 transcription factor network, IL23-mediated signaling events, Jak-STAT signaling pathway, Osteoclast differentiation
PRDM1	PR domain containing 1, with ZNF domain	1.829	1.48E-03	textmining	Direct p53 effectors
HBEGF	heparin-binding EGF-like growth factor	1.825	2.94E-03	curated databases, textmining	GPCR signaling, Signaling by GPCR, ErbB receptor signaling network, ErbB signaling pathway
PDE4B	phosphodiesterase 4B, cAMP-specific	1.810	7.73E-03	experimentally determined, textmining	Signaling by GPCR, GPCR downstream signaling
PLAUR	plasminogen activator, urokinase receptor	1.771	2.63E-04	co-expresssion, curated databases, textmining	Validated transcriptional targets of AP1 family members Fra1 and Fra2
CD274	CD274 molecule	1.768	4.26E-04	co-expression, textmining	None
ZFP36	zinc finger protein 36, C3H type, homolog (mouse)	1.745	2.00E-03	co-expresssion, curated databases, textmining	None
HCAR2	hydroxycarboxylic acid receptor 2	1.727	1.48E-03	curated databases, textmining	GPCR ligand binding, Signaling by GPCR, Class A/1 (Rhodopsin-like receptors), GPCR downstream signaling, G alpha (i) signalling events
PMAIP1	phorbol-12-myristate-13-acetate-induced protein 1	1.695	1.48E-03	textmining	Direct p53 effectors
CLDN1	Rho family GTPase 1	1.691	1.10E-02	textmining	None
RND1	Rho family GTPase 1	1.691	1.10E-02	experimentally determined, textmining	None
LMO7	LIM domain 7	1.665	3.59E-03	curated databases, textmining	None

FOXA1	forkhead box A1	1.645	5.75E-03	textmining	Direct p53 effectors
RGS2	regulator of G-protein signaling 2, 24kDa	1.637	3.25E-02	curated databases, textmining	GPCR signaling, Signaling by GPCR, GPCR downstream signaling, G alpha (i) signalling events
CCL20	chemokine (C-C motif) ligand 20	1.589	2.82E-02	co-expresssion, curated databases, textmining	Cytokine-cytokine receptor interaction, Chemokine receptors bind chemokines, GPCR ligand binding, Signaling by GPCR, Class A/1 (Rhodopsin-like receptors), Peptide ligand-binding receptors, GPCR downstream signaling, G alpha (i) signalling events
CXCL1	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	1.524	1.09E-02	co-expression, protein homology, curated databases, textmining	Cytokine-cytokine receptor interaction, IL23-mediated signaling events, Chemokine receptors bind chemokines, GPCR ligand binding, Signaling by GPCR, Class A/1 (Rhodopsin-like receptors), NOD-like receptor signaling pathway, Peptide ligand-binding receptors, Amoebiasis, GPCR downstream signaling, G alpha (i) signalling events
FOSL1	FOS-like antigen 1	1.517	1.48E-03	experimentally determined, co-expression, protein homology, curated databases, textmining	AP-1 transcription factor network, Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Validated transcriptional targets of AP1 family members Fra1 and Fra2, Calcium signaling in the CD4+ TCR pathway, Osteoclast differentiation
MMP10	matrix metallopeptidase 10 (stromelysin 2)	1.514	4.00E-02	experimentally determined, co-expression, protein homology, curated databases, textmining	None
EGR3	early growth response 3	1.502	7.12E-03	experimentally determined, co-expression, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes
VGLL3	vestigial like 3 (Drosophila)	1.489	1.48E-03	co-expression, textmining	None
IL13RA2	interleukin 13 receptor, alpha 2	1.480	1.48E-03	curated databases, co-expression, textmining	Jak-STAT signaling pathway
GADD45B	growth arrest and DNA-damage-inducible, beta	1.454	1.43E-02	co-expression, textmining	None
ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif, 1	1.445	3.43E-02	textmining	None

JUN	jun proto-oncogene	1.440	3.59E-03	experimentally determined, co-expression, curated databases, textmining	AP-1 transcription factor network, ATF-2 transcription factor network, Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Validated transcriptional targets of AP1 family members Fra1 and Fra2, Calcium signaling in the CD4+ TCR pathway, Signal transduction through il1r, Direct p53 effectors, Osteoclast differentiation, Leishmaniasis, ErbB signaling pathway
IL1B	interleukin 1, beta	1.439	1.17E-02	experimentally determined, co-expression, curated databases, textmining	Cytokine-cytokine receptor interaction, GPCR signaling, IL23-mediated signaling events, NOD-like receptor signaling pathway, Amoebiasis, Hematopoietic cell lineage, Signal transduction through il1r, Graft-versus-host disease, Osteoclast differentiation, Nfkb activation by nontypeable hemophilus influenzae, Malaria, Leishmaniasis
GRHL1	grainyhead-like 1 (Drosophila)	1.407	4.27E-02	experimentally determined, protein homology, textmining	None
MMP1	matrix metallopeptidase 1 (interstitial collagenase)	1.406	7.25E-03	protein homology, curated databases, textmining	AP-1 transcription factor network, Validated transcriptional targets of AP1 family members Fra1 and Fra2
MAFF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	1.402	1.35E-02	experimentally determined, co-expression, textmining	None
BMP2	bone morphogenetic protein 2	1.368	2.94E-03	curated databases, textmining	Cytokine-cytokine receptor interaction, GPCR signaling
NRG1	neuregulin 1	1.352	4.50E-03	co-expresssion, curated databases, textmining	GPCR signaling, ErbB receptor signaling network, ErbB signaling pathway
EDN1	endothelin 1	1.351	3.17E-02	co-expresssion, curated databases, textmining	AP-1 transcription factor network, GPCR signaling, GPCR ligand binding, Signaling by GPCR, Class A/1 (Rhodopsin-like receptors), Peptide ligand-binding receptors, GPCR downstream signaling
PELI1	pellino E3 ubiquitin protein ligase 1	1.314	5.75E-03	curated databases, textmining	None
ADRB2	adrenoceptor beta 2, surface	1.309	5.81E-03	experimentally determined, curated databases, textmining	GPCR ligand binding, Signaling by GPCR, Class A/1 (Rhodopsin-like receptors), GPCR downstream signaling
RND3	Rho family GTPase 3	1.299	8.48E-03	experimentally determined, co-expression, textmining	None
HAS2	hyaluronan synthase 2	1.296	3.09E-02	textmining	None

ADAMTS6	ADAM metallopeptidase with thrombospondin type 1 motif, 6	1.265	9.78E-03	textmining	None
GRHL3	grainyhead-like 3 (Drosophila)	1.242	2.72E-03	experimentally determined, protein homology, textmining	None

Table S3: Metadata for transcriptome interaction network and pathway analysis of 5448 intracellularly infected Tepi cells in comparison to JRS4 infected cells.

Gene symbol	**Full name**	**Log2FC gene expression in comparison to JRS4-infected cells**	**Adjusted P-value**	**Protein-protein interaction data type from Stringdb.com**	**Upregulated pathways from Innatedb.com**
FOSB	FBJ murine osteosarcoma viral oncogene homolog B	3.484	3.04E-04	experimentally determined, textmining	Osteoclast differentiation, AP-1 transcription factor network
EGR4	early growth response 4	3.457	1.02E-03	experimentally determined, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Downstream signaling in naïve CD8+ T cells
IRF1	interferon regulatory factor 1	3.390	6.49E-04	experimentally determined, coexpression, curated databases, textmining	Glucocorticoid receptor regulatory network, Cytokine Signaling in Immune system, IL6-mediated signaling events, Innate Immune System
TRAF1	TNF receptor-associated factor 1	3.253	6.49E-04	experimentally determined, coexpression, curated databases, textmining	CD40/CD40L signaling, Tnfr2 signaling pathway, HIV-1 Nef: Negative effector of Fas and TNF-alpha, RANKL, TNF receptor signaling pathway, TWEAK
BIRC3	baculoviral IAP repeat containing 3	2.712	6.49E-04	experimentally determined, coexpression, curated databases, textmining	CD40/CD40L signaling, NOD-like receptor signaling pathway, HIV-1 Nef: Negative effector of Fas and TNF-alpha, Toll-Like Receptors Cascades, Activated TLR4 signalling, Toll Like Receptor 4 (TLR4) Cascade, TNF receptor signaling pathway, Innate Immune System

TNF	tumor necrosis factor	2.622	6.54E-04	coexpression, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes, Osteoclast differentiation, Cytokine-cytokine receptor interaction, MAPK signaling pathway, NOD-like receptor signaling pathway, JAK STAT pathway and regulation, HIV-1 Nef: Negative effector of Fas and TNF-alpha, Downstream signaling in naïve CD8+ T cells, T cell receptor signaling pathway, Hematopoietic cell lineage, Nfat and hypertrophy of the heart, Toll-like receptor signaling pathway, IL23-mediated signaling events, TNF receptor signaling pathway, TWEAK, Adipocytokine signaling pathway, GPCR signaling
PTX3	pentraxin 3, long	2.578	3.73E-03	textmining	None
NFKBIE	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon	2.468	2.12E-04	experimentally determined, coexpression, textmining	T cell receptor signaling pathway, Adipocytokine signaling pathway
CD83	CD83 molecule	2.433	1.09E-03	coexpression, textmining	None
EGR2	early growth response 2	2.407	8.64E-04	experimentally determined, coexpression, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes, IL4-mediated signaling events
GDF15	growth differentiation factor 15	2.350	2.50E-03	textmining	Direct p53 effectors
CCL20	chemokine (C-C motif) ligand 20	2.308	1.01E-03	curated databases, coexpression, textmining	Cytokine-cytokine receptor interaction, Class A/1 (Rhodopsin-like receptors), GPCR ligand binding, Peptide ligand-binding receptors, Chemokine receptors bind chemokines, Signaling by GPCR, GPCR downstream signaling
LIF	leukemia inhibitory factor	2.261	2.55E-03	curated databases, textmining	Cytokine-cytokine receptor interaction, JAK STAT pathway and regulation, Direct p53 effectors, Nfat and hypertrophy of the heart, GPCR signaling
MAFF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	2.203	6.49E-04	experimentally determined, textmining	None

NR4A3	nuclear receptor subfamily 4, group A, member 3	2.202	4.58E-03	experimentally determined, textmining	None
BCL2A1	BCL2-related protein A1	2.139	8.09E-04	experimentally determined, curated databases, textmining	None
PPP1R15A	protein phosphatase 1, regulatory subunit 15A	2.136	1.26E-04	textmining	None
TNFAIP2	tumor necrosis factor, alpha-induced protein 2	2.114	6.85E-04	textmining	None
NR4A1	nuclear receptor subfamily 4, group A, member 1	2.107	2.78E-03	experimentally determined, coexpression, textmining	MAPK signaling pathway, Glucocorticoid receptor regulatory network, TCR, Innate Immune System
HBEGF	heparin-binding EGF-like growth factor	2.044	6.71E-04	curated databases, textmining	Signaling by GPCR, Nfat and hypertrophy of the heart, GPCR signaling, Innate Immune System
CX3CL1	chemokine (C-X3-C motif) ligand 1	2.007	6.49E-04	textmining	Cytokine-cytokine receptor interaction, Class A/1 (Rhodopsin-like receptors), GPCR ligand binding, Peptide ligand-binding receptors, Chemokine receptors bind chemokines, Direct p53 effectors, Signaling by GPCR
GEM	GTP binding protein overexpressed in skeletal muscle	1.951	8.52E-03	experimentally determined, textmining	None
EGR1	early growth response 1	1.894	3.28E-02	experimentally determined, curated databases, protein homology, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes, AP-1 transcription factor network, Glucocorticoid receptor regulatory network, Downstream signaling in naïve CD8+ T cells, Oncostatin_M, TCR, Cytokine Signaling in Immune system
PTGER4	prostaglandin E receptor 4 (subtype EP4)	1.891	7.20E-04	textmining	Class A/1 (Rhodopsin-like receptors), GPCR ligand binding, Signaling by GPCR, GPCR downstream signaling
ICAM1	intercellular adhesion molecule 1	1.872	1.22E-03	curated databases, coexpression, textmining	Glucocorticoid receptor regulatory network, Toll-Like Receptors Cascades, Activated TLR4 signalling, Toll Like Receptor 4 (TLR4) Cascade, Cytokine Signaling in Immune system, Toll-like receptor signaling pathway, Innate Immune System

BDKRB1	bradykinin receptor B1	1.866	6.73E-03	curated databases	Class A/1 (Rhodopsin-like receptors), GPCR ligand binding, Peptide ligand-binding receptors, Signaling by GPCR, GPCR downstream signaling
GADD45B	growth arrest and DNA-damage-inducible, beta	1.825	1.03E-03	textmining	MAPK signaling pathway, IL12-mediated signaling events
CXCL2	chemokine (C-X-C motif) ligand 2	1.820	3.96E-03	coexpression, curated databases	Cytokine-cytokine receptor interaction, NOD-like receptor signaling pathway, Class A/1 (Rhodopsin-like receptors), GPCR ligand binding, Peptide ligand-binding receptors, Chemokine receptors bind chemokines, Signaling by GPCR, GPCR downstream signaling
EGR3	early growth response 3	1.780	6.68E-04	experimentally determined, textmining	Calcineurin-regulated NFAT-dependent transcription in lymphocytes
TNFAIP3	tumor necrosis factor, alpha-induced protein 3	1.699	1.70E-03	experimentally determined, coexpression, textmining	CD40/CD40L signaling, NOD-like receptor signaling pathway, Tnfr2 signaling pathway, TNF receptor signaling pathway, Innate Immune System
NFKBIZ	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta	1.647	2.48E-03	experimentally determined, textmining	None
CORO6	coronin 6	1.621	1.22E-03	experimentally determined, coexpression, textmining	None
LRIG3	leucine-rich repeats and immunoglobulin-like domains 3	-1.608	1.02E-03	experimentally determined, textmining	None
ACTL10	actin-like 10	-1.765	2.91E-03	experimentally determined, coexpression, textmining	None
HIST1H2BF	histone cluster 1, H2bf	-1.959	4.94E-02	experimentally determined, coexpression, textmining	None