Supplementary materials

Combined treatment with HMGN1 and anti-CD4 depleting antibody reverses T cell exhaustion and exerts robust anti-tumor effects in mice

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7 figures, 3 methods, and 4 tables

Supplementary figures

Figure S1

A

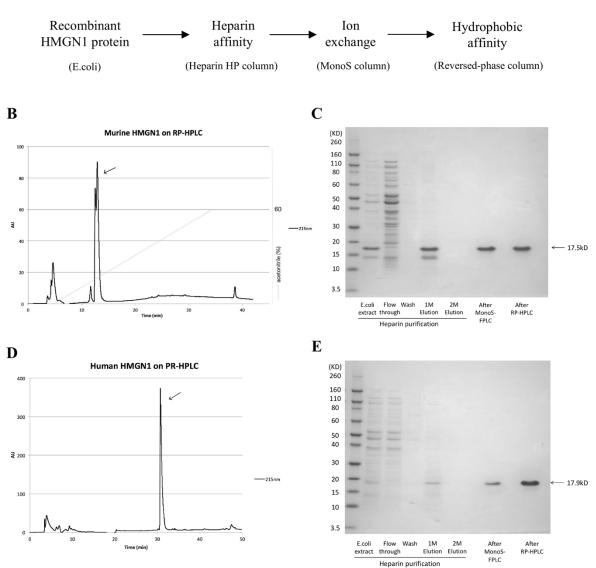


Figure S1. The purification of recombinant HMGN1 proteins. (A) The flowchart of purifying recombinant HMGN1 protein. **(B, D)** In reverse phase HPLC (RP-HPLC), the linear fractions with the highest absorbance unit (AU) were collected, and identified as murine HMGN1 (mH) or human HMGN1 (hH) by N-terminal amino acid sequencing. **(C, E)** MES buffered 4-12% Bis-Tris SDS-PAGE analysis of stepwise purification of mH and hH.

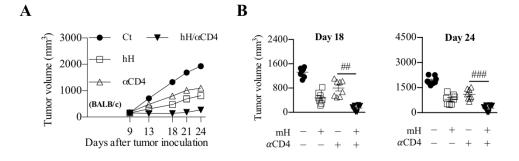


Figure S2. Administration of human HMGN1 (hH) with anti-CD4 depleting antibody (α CD4) exerted anti-tumor effects in mice. The hH (at a dose of 0.16 µg/ injection) was administered intraperitoneally on days 9, 14, 17, and 20 after tumor inoculation. The α CD4 (at a dose of 200 µg/ injection) was injected intraperitoneally on days 5 and 9 after tumor inoculation. (A) The quantitative analysis of tumor growth and tumor progression for each mouse until 24 days after treatment. (B) The tumor volume of each mouse on day 18 and day 24. Tumor growth is represented as mean ± SEM. #, P<0.05, ##, P<0.01, ###, p<0.001 for a Student's *t*-test comparing mH/ α CD4-treated and α CD4-treated groups.



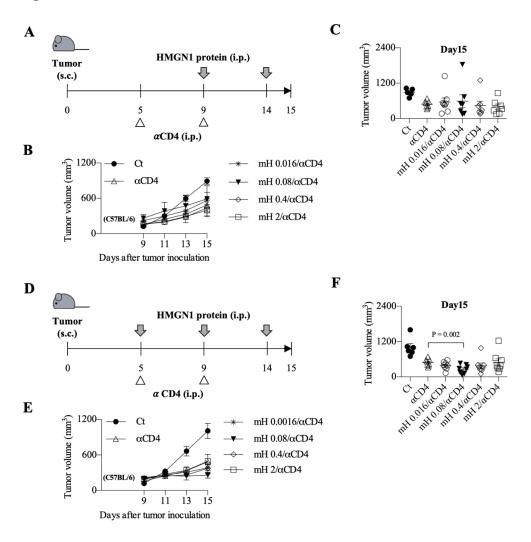


Figure S3. Administration of murine HMGN1 with anti-CD4 antibody exerted anti-tumor effects in melanoma model. (A) The administration of twice α CD4 on day 5, 9 and twice mHMGN1 on day 9, 14. (B, C) The tumor growth rate and the tumor volume after mHMGN1/ α CD4 treatment. (D) The optimized administration of twice α CD4 on days 5, 9 and three times mHMGN1 on days 5, 9, 14. (E, F) The tumor growth rate and the tumor volume after optimized mHMGN1/ α CD4 treatment. Tumor growth is representative of three independent experiments with at least eight mice per group. Data are presented as mean ± SEM.

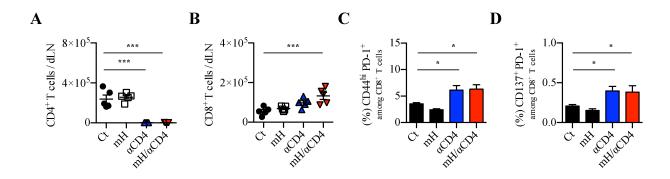


Figure S4. Flow cytometry analysis of T cell populations in the draining lymph node (dLN) from Colon26 tumor-bearing mice on day 13 after tumor inoculation. (A) The number of CD4⁺ T cells. (B) The number of CD8⁺ T cells. (C, D) The percentile of CD137⁺PD-1⁺ and CD44^{hi} PD-1⁺ among CD8⁺ T cells. Each result is representative of three independent experiments with at least four mice per group. Data are presented as mean \pm SEM. *, P<0.05, **, P<0.01, ***, P<0.001 for a dunnett's *post hoc* test (compared with control).

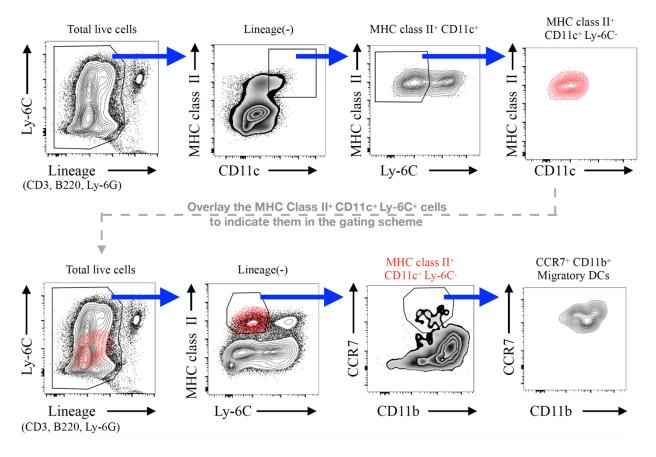


Figure S5. Gating scheme of CCR7⁺ CD11b⁺ migratory dendritic cells (DCs). Representative

flow cytometry plots showing gating scheme for CCR7⁺ CD11b⁺ migratory DCs.

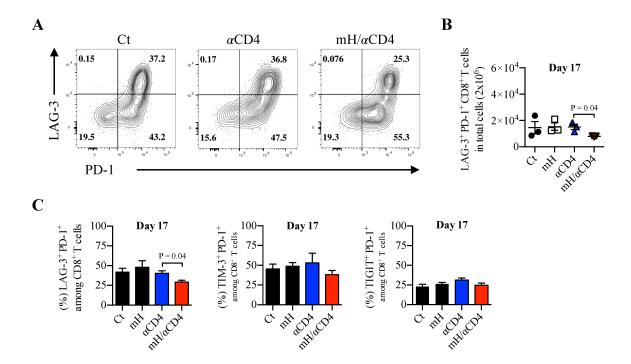


Figure S6. Flow cytometry analysis of exhausted CD8⁺ T cell populations in the tumor from tumor-bearing mice on day 17 after treatment. (A, B) The compartment and the cell number of LAG-3⁺ PD-1⁺ CD8⁺ T cells in the tumor. (C) The percentage of LAG⁺ PD-1⁺, TIM-3⁺ PD-1⁺, and TIGIT⁺ PD-1⁺ among CD8⁺ T cells. Each result is representative of three independent experiments with at least four mice per group. Data are presented as mean \pm SEM. p values in the figure indicate the Student's *t*-test comparing mH/ α CD4-treated and α CD4-treated groups.

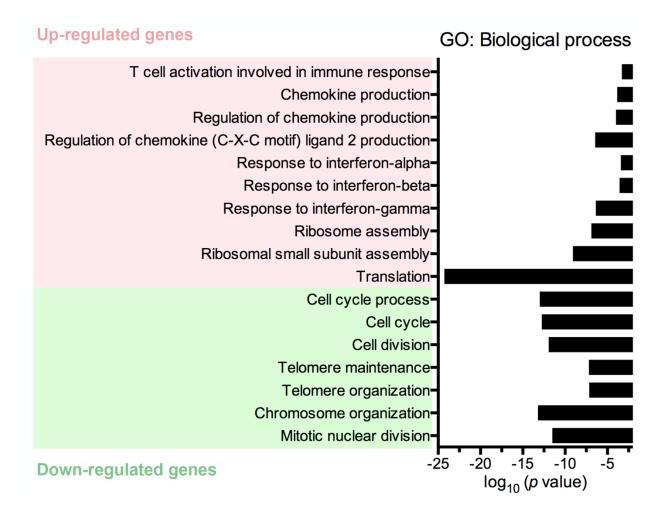


Figure S7. CD8 T cell transcriptome analysis revealed the promotion of activation after HMGN1/ α CD4 treatment. Biological events associated with 517 DEGs (157 up-regulated and 364 down-regulated) were explored and grouped using Cytoscape and ClueGO plugin. Significantly enriched Gene ontology (GO) leading terms are shown on the left side of the graph. The statistical significance of each enrichment (*p* value, log₁₀) was represented by bar graph.

Supplementary methods

Supplementary method 1. Production and purification of HMGN1 in E. coli

The expression pET-17b plasmid with murine HMGN1 coding region (122-412) or human HMGN1 coding region (205-507) was transformed into BL21 StarTM (DE3) E. coli (Thermo Fisher Scientific) by heat shock method. The single colony was picked up and pre-cultivated in a LB/ampicillin medium until the OD600 absorbance reaches 0.6. Added isopropyl β-D-1thiogalactopyranoside (IPTG, final concentration equal to 1 mM) into culture medium and cultivated the cells for 4 hours. The cell pellet was collected by centrifugation at 15,000 x g for 5 min, and then the soluble proteins were extracted from cell pellet by sonication. To purify the recombinant HMGN1 protein from soluble proteins, the following procedures were administered to each subject in the order mentioned. (1) For heparin-affinity chromatography, the soluble proteins were applied to a HiTrapTM Heparin HP column (5 ml, GE Healthcare) equilibrated with 10 mM sodium phosphate buffer, pH 7.0 (NaPB) containing 0.2 M NaCl. After washing the column, HMGN1 was eluted by NaPB with 1 M NaCl. (2) For cation exchange chromatography, the eluted HMGN1 from heparin column was loaded into a Mono S HR 5/5 (5 x 50 mm, Pharmacia Biotech) equipped to a FPLC system (Pharmacia Biotech), equilibrated with NaPB buffer, and adjusted the flow rate to 1 ml/min. The HMGN1 fractions were eluted by a linear gradient from 0.2 to 1.0 M NaCl in NaPB. (3) For hydrophobic interaction chromatography, the HMGN1 fractions from MonoS-FPLC were directly referred to a reverse phase RP-304 column (4.6 x 205 mm, C4, BioRad) equipped to a HPLC system (Gilson). The HMGN1 was purified by a linear gradient of acetonitrile from 0 to 60% in water with 0.01% trifluoroacetic acid (TFA). The acetonitrile was further removed from the purified sample by freeze-drying. Highly purified recombinant HMGN1 was examined the endotoxin level and was kept frozen at -80°C.

Supplementary method 2. 3'end Serial Analysis of Gene Expression (SAGE) sequencing library preparation

Three minutes before collecting tumor tissues, intravascular leukocytes were stained by intravenous injection of FITC anti-CD45 antibody. CD8⁺ T cells from tumor tissue were labeled with APC anti-CD8 antibody (clone: 53-6.7; BioLegend, USA), anti-APC microbeads (Miltenyl Biotec, Germany), and lineage antibody cocktail (FITC anti-CD11b, FITC anti-B220, FITC anti-CD49b, FITC anti-Ter119, and Pacific blue anti-CD4 antibodies). Labeled CD8⁺ T cells were separated by using an autoMACS cell separator (Miltenyl Biotec, Germany). Then, CD8⁺ T cells were further purified from lineage sorting (CD45⁻CD11b⁻ B220⁻CD49b⁻Ter119⁻CD4⁻CD8⁺) by FACSAria II Cell Sorter (BD Biosciences, USA).

Purity of isolated CD8⁺ T cells among live cells was over 99% for RNA transcriptome analysis. Total RNA was extracted from 10,000 CD8⁺ T cells of each sample and stored in lysis/binding buffer (Thermo Fisher Scientific, USA). Messenger RNA (mRNA) was isolated from total RNA by Dynabeads M-270 streptavidin with biotin-oligo (dT)25 (Thermo Fisher Scientific, USA). First- and second-strand cDNA synthesis was performed by Superscript reverse transcriptase IV (Thermo Fisher Scientific, USA) and Kapa HiFi DNA polymerase (Roche, Switzerland). While capturing on the beads, cDNA was digested with restriction endonuclease NlaIII (Thermo Fisher Scientific, USA), which cleaved the 3'end CATG/GTAC restriction site. Each cDNA fragment carrying the 3'CATG overhang was ligated to an adapter carrying common sequence 1 (CS1) and EcoP15I recognition site (5'-CAGCCAG-3'), and sequentially digested by EcoP15I restriction endonuclease to generate a 27-bp sequence with 5' end overhang (2-bp). Next, another adaptor carrying CS2 and sequencing primer site was ligated to the 5' end overhang of 27-bp sequence, and the 46-bp ligation product was obtained by MinElute PCR purification kit (Qiagen, Germany). Finally, an 8-cycle PCR step was performed to enrich for the desired cDNA library molecules, and those cDNA library products were purified by size selection using AMPure XP beads (Beckman Coulter, USA). We used Ion Torrent (Thermo Fisher Scientific, USA) to prepare cDNA template, the template which further analyzed by Ion Proton Sequencer (Thermo Fisher Scientific, USA).

Supplementary tables

Species	Description	Abbreviation	Amino acid sequence
			1- MPKRKVSADGAAKAEPKRRS
			21- ARLSAKPAPAKVDAKPKKAA
Murine	HMGN1 (1-96 a.a)	mH	41- GKDKASDKKVQIKGKRGAKG
			61- KQADVADQQTTELPAENGET
			81- ENQSPASEEEKEAKSD
			1- MPKRKVSSAEGAAKEEPKRR
	h HMGN1 (1-100 a.a.) hH		21- SARLSAKPPAKVEAKPKKAA
Human		hH	41- AKDKSSDKKVQTKGKRGAKG
			61- KQAEVANQETKEDLPAENGE
			81- TKTEESPASDEAGEKEAKSD

 Table S1
 The list of recombinant proteins and peptides

Antibody	Clone	Antibody	Clone
CD3e	145-2C11	TIGIT	1G9
CD4	RM4-4	TIM-3	RMT3-23
CD8a	53-6.7	PD-1 / CD279	RMP1-30
CD11b	M1/70	Ly-6C	HK1.4
CD11c	N418	Ly-6G	1A8
CD28	37.51	CCR-7	4B12
CD44	IM7	IL-2	JES6-5H4
CD45	30-F11	IFN-γ	XMG1.2
B220	RA3-6B2	TNF-α	MP6-XT22
CD49b / Pan NK	DX5	Isotype Controls	
CD90.1	OX-7	Mouse IgG	MOPC-21
CD137	17B5	Rat IgG1	HRPN
ICOS / CD278	C398.4A	Rat IgG2b	LTF-2
LAG-3	eBioC9B7W	American Hamster IgG	HTK888

 Table S2
 Antibodies for flow cytometry

Monoclonal antibodies (mAbs) were purchased from BD bioscience, BioLegend, eBioscience or Tonbo bioscience.

Name	Sequences (5' – 3')	Species	Marker
Cytotoxic T-lymphocyte-associated protein 4 (Ctla4), F	TCATGTACCCACCGCCATAC	mus musculus	Eurofins (JP)
Cytotoxic T-lymphocyte-associated protein 4 (Ctla4), R	CCCCAAGCTAACTGCGACAA	mus musculus	Eurofins (JP)
Cytotoxic T-lymphocyte-associated protein 4 (Ctla4), Probe	TTGTGGGCATGGGCAACGGGACGCAGA	mus musculus	Eurofins (JP)
Glyceraldehyde-3-phosphate dehydrogenase (Gapdh), F	AGTATGACTCCACTCACGGCAA	mus musculus	Sigma-Aldrich (USA)
Glyceraldehyde-3-phosphate dehydrogenase (Gapdh), R	TCTCGCTCCTGGAAGATGGT	mus musculus	Sigma-Aldrich (USA)
Lymphocyte-activation gene 3 (Lag3), F	CACCTGTAGCATCCATCTGC	mus musculus	Eurofins (JP)
Lymphocyte-activation gene 3 (Lag3), R	CCAGGTAACCCGAAGGATTT	mus musculus	Eurofins (JP)
Programmed cell death 1 (Pdcd1), F	TGCAGTTGAGCTGGCAAT	mus musculus	Eurofins (JP)
Programmed cell death 1(Pdcd1), R	GGCTGGGTAGAAGGTGAGG	mus musculus	Eurofins (JP)
TIM-3 (Havcr2), F	TTTTCAGGTCTTACCCTCAACTG	mus musculus	Eurofins (JP)
TIM-3 (Havcr2), R	CATAAGCATTTTCCAATGACCTT	mus musculus	Eurofins (JP)

Table S3 Primers for quantitative real-time PCR

REGG.03010 Rboome 4.985.44 98.00 GO.0006412 translation 5.48E-25 37.00 GO.0006313 peptide biosynthatic process 6.51E-23 37.00 GO.0006310 peptide metabolic process 1.38E-13 37.00 GO.0006310 celtular amide metabolic process 1.38E-13 37.00 GO.0006310 organomitrogen compound biosynthatic process 1.44E-17 40.00 GO.0006211 ribosomal small subunit assembly 8.26E-10 6.00 GO.0002241 ribosome simuli subunit biogenesis 2.07E-08 1.30E GO.0002251 ribosome sasembly 1.28E-07 7.00 GO.0002261 ribosome sasembly 2.07E-08 4.00 GO.000231 response to interferon-garma 4.20E-07 8.00 GO.0002321 response to interferon-garma 4.32E-07 4.00 GO.0002321 response to interferon-garma 4.20E-07 8.00 GO.0002321 response to interferon-garma 4.32E-05 8.00 GO.0002321 response to interferon-garma 4.3	ID	GO term (upregulated)	Term <i>p</i> value	Nr. genes
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GC:0034341 response to interferon-gamma 4.20E-07 8.00 GC:0006123 mitochondrial electron transport, cytochrome c to oxygen 8.37E-07 4.00 GC:0072567 chemokine (C-X-C motif) ligand 2 production 8.37E-07 4.00 GC:0002618 ribonucleoprotein complex assembly 8.53E-06 9.00 GC:00071826 ribonucleoprotein complex assembly 8.53E-06 9.00 GC:00071826 ribonucleoprotein complex subunit organization 1.35E-05 9.00 GC:0004377 mitochondrial ATP synthesis coupled electron transport 2.27E-05 5.00 GC:0004596 regulation of viral entry into host cell 3.68E-05 4.00 GC:002604 Huntington's disease 4.28E-05 8.00 GC:0022020 regulation of chemokine production 1.03E-04 5.00 GC:0022041 regulation of chemokine production 1.03E-05 7.00 GC:00220203 regulation of chemokine production 1.03E-04 5.00 GC:0022040 regulation of chemokine production 1.03E-04 5.00 GC:00220204 regulation of chemokine producti	GO:0042255	ribosome assembly	1.28E-07	7.00
GO:0006123mitochondrial electron transport, cytochrome c to oxygen8.37E-074.00GO:0072567chemokine (C-X-C motif) ligand 2 production8.37E-074.00GO:0022618ribonucleoprotein complex assembly8.53E-069.00GO:0071826ribonucleoprotein complex assembly8.53E-069.00GO:0071826ribonucleoprotein complex subunit organization1.35E-059.00GO:0071826ribonucleoprotein complex subunit organization1.35E-059.00GO:000364rRNA processing3.05E-058.00GO:00042773ATP synthesis coupled electron transport3.27E-055.00GO:004596regulation of viral entry into host cell3.68E-054.00GO:1002253regulation of intrinsic apototic signaling pathway by p53 class mediator4.23E-058.00KEGG:05016Huntington's disease4.28E-058.00GO:0022642regulation of chemokine production1.03E-045.00GO:0022044respiratory electron transport chain1.43E-045.00GO:0022044respiratory electron transport chain1.43E-043.00GO:002204respiratory electron transport along microtubule1.45E-043.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0047497mitochondrion localization, microtubule-mediated1.45E-043.00GO:0046597negative regulation of viral entry into host cell2.0	GO:2000341	regulation of chemokine (C-X-C motif) ligand 2 production	3.59E-07	4.00
GO:0072567 chemokine (C-X-C motif) ligand 2 production 8.37E-07 4.00 GO:0022618 ribonucleoprotein complex assembly 8.53E-06 9.00 GO:2000343 positive regulation of chemokine (C-X-C motif) ligand 2 production 9.43E-06 3.00 GO:0071826 ribonucleoprotein complex subunit organization 1.35E-05 9.00 GO:0071826 ribonucleoprotein complex subunit organization 1.35E-05 9.00 GO:0042775 mitochondrial ATP synthesis coupled electron transport 2.27E-05 5.00 GO:0042773 ATP synthesis coupled electron transport 3.27E-05 5.00 GO:0042656 regulation of viral entry into host cell 3.68E-05 4.00 GO:0042657 regulation of intrinsic apoptotic signaling pathway by 53 class mediator 4.23E-05 8.00 KEGG:04932 Non-alcoholic fatty liver disease (NAFLD) 6.25E-05 7.00 GO:0032602 regulation of chemokine production 1.43E-04 5.00 GO:0032602 chemokine production 1.43E-04 3.00 GO:0032602 chemokine production 1.45E-04 3.00 <t< td=""><td>GO:0034341</td><td>response to interferon-gamma</td><td>4.20E-07</td><td>8.00</td></t<>	GO:0034341	response to interferon-gamma	4.20E-07	8.00
GO:0022618 ribonucleoprotein complex assembly 8.53E-06 9.00 GO:000343 positive regulation of chemokine (C-X-C motif) ligand 2 production 9.43E-06 3.00 GO:00071826 ribonucleoprotein complex subunit organization 1.35E-05 9.00 GO:00042775 mitochondrial ATP synthesis coupled electron transport 2.27E-05 5.00 GO:0042773 ATP synthesis coupled electron transport 3.05E-05 8.00 GO:0046596 regulation of viral entry into host cell 3.68E-05 4.00 GO:0022618 Huntington's disease 4.28E-05 8.00 GO:0026042 regulation of intrinsic apoptotic signaling pathway by p53 class mediator 4.23E-05 4.00 GO:0022601 Huntington's disease 4.28E-05 8.00 60:0022904 respiratory electron transport chain 1.03E-04 5.00 60:0032602 chemokine production 1.03E-04 5.00 60:0032602 chemokine production 1.43E-04 5.00 60:0032602 chemokine production 1.43E-04 3.00 60:004344 setablishment of mitochondrion localization, microtubule-mediated 1.45E-04 3.00 6	GO:0006123	mitochondrial electron transport, cytochrome c to oxygen	8.37E-07	4.00
GO:2000343 positive regulation of chemokine (C-X-C motif) ligand 2 production 9.43E-06 3.00 GO:0071826 ribonucleoprotein complex subunit organization 1.35E-05 9.00 GO:0017826 ribonucleoprotein complex subunit organization 1.35E-05 9.00 GO:0042775 mitochondrial ATP synthesis coupled electron transport 2.27E-05 5.00 GO:0042773 ATP synthesis coupled electron transport 3.27E-05 5.00 GO:0046596 regulation of viral entry into host cell 3.68E-05 4.00 GO:01902253 regulation of intrinsic apoptotic signaling pathway by p53 class mediator 4.23E-05 8.00 KEGG:04932 Non-alcoholic fatty liver disease (NAFLD) 6.25E-05 7.00 GO:0022204 regulation of chemokine production 1.03E-04 5.00 GO:0032602 chemokine production 1.43E-04 5.00 GO:004443 establishment of mitochondrion localization, microtubule-mediated 1.45E-04 3.00 GO:0046597 negative regulation of viral entry into host cell 2.09E-04 3.00 GO:0046597 negative regulation of viral entry into host cell <t< td=""><td>GO:0072567</td><td>chemokine (C-X-C motif) ligand 2 production</td><td>8.37E-07</td><td>4.00</td></t<>	GO:0072567	chemokine (C-X-C motif) ligand 2 production	8.37E-07	4.00
GO:0071826ribonucleoprotein complex subunit organization1.35E-059.00GO:0042775mitochondrial ATP synthesis coupled electron transport2.27E-055.00GO:006364rRNA processing3.05E-058.00GO:0042773ATP synthesis coupled electron transport3.27E-055.00GO:0046596regulation of viral entry into host cell3.68E-054.00GO:1902253regulation of intrinsic apoptotic signaling pathway by p53 class mediator4.23E-058.00KEGG:05016Huntington's disease4.28E-058.00KEGG:04932Non-alcoholic fatty liver disease (NAFLD)6.25E-057.00GO:0032642regulation of chemokine production1.03E-045.00GO:0032642regulation of chemokine production1.43E-045.00GO:0032602chemokine production1.43E-043.00GO:0034643establishment of mitochondrion localization, microtubule-mediated1.45E-043.00GO:0047497mitochondrion transport along microtubule1.45E-043.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0045624positive regulation of viral entry into host cell2.09E-043.00GO:0045697negative regulation of viral entry into host cell2.09E-043.00GO:0045697negative regulation of viral entry into host cell2.09E-043.00GO:0045697negative regulation of viral entry int	GO:0022618	ribonucleoprotein complex assembly	8.53E-06	9.00
G0:0042775mitochondrial ATP synthesis coupled electron transport2.27E-055.00G0:0006364rRNA processing3.05E-058.00G0:0042773ATP synthesis coupled electron transport3.27E-055.00G0:0046596regulation of viral entry into host cell3.68E-054.00G0:1902253regulation of intrinsic apoptotic signaling pathway by p53 class mediator4.23E-054.00KEGG:05016Huntington's disease4.28E-058.00KEGG:04932Non-alcoholic fatty liver disease (NAFLD)6.25E-057.00G0:0032642regulation of chemokine production1.03E-045.00G0:0022904respiratory electron transport chain1.43E-045.00G0:0032602chemokine production1.43E-043.00G0:0032602chemokine production1.43E-043.00G0:0047497mitochondrion localization, microtubule-mediated1.45E-043.00G0:0047497mitochondrion transport along microtubule1.82E-045.00G0:004597negative regulation of viral entry into host cell2.09E-043.00G0:0045624positive regulation of viral entry into host cell2.09E-043.00G0:004564positive regulation of viral genome replication2.13E-044.00G0:004567negative regulation of viral genome replication2.13E-044.00G0:0045624positive regulation of viral genome replication2.13E-044.00G0:004567iequitive regulation of viral genome replication2.28E-045.00	GO:2000343	positive regulation of chemokine (C-X-C motif) ligand 2 production	9.43E-06	3.00
GO:0006364rRNA processing3.05E-058.00GO:0042773ATP synthesis coupled electron transport3.27E-055.00GO:0046596regulation of viral entry into host cell3.68E-054.00GO:1902253regulation of intrinsic apoptotic signaling pathway by p53 class mediator4.23E-054.00KEGG:05016Huntington's disease4.28E-058.00KEGG:04932Non-alcoholic fatty liver disease (NAFLD)6.25E-057.00GO:0032642regulation of chemokine production1.03E-045.00GO:0032642regulation of chemokine production1.43E-045.00GO:0032602chemokine production1.43E-045.00GO:0034643establishment of mitochondrion localization, microtubule-mediated1.45E-043.00GO:0047497mitochondrion transport along microtubule1.45E-043.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0045624positive regulation of viral genome replication2.13E-044.00GO:0045671negative regulation of viral genome replication2.13E-045.00GO:0022900electron transport chain2.13E-045.00	GO:0071826	ribonucleoprotein complex subunit organization	1.35E-05	9.00
GO:0042773ATP synthesis coupled electron transport3.27E-055.00GO:0046596regulation of viral entry into host cell3.68E-054.00GO:1002253regulation of intrinsic apoptotic signaling pathway by p53 class mediator4.23E-054.00KEGG:05016Huntington's disease4.28E-058.00KEGG:04932Non-alcoholic fatty liver disease (NAFLD)6.25E-057.00GO:0032642regulation of chemokine production1.03E-045.00GO:0032642regulation of chemokine production1.43E-045.00GO:0032622chemokine production1.43E-045.00GO:0032632chemokine production1.43E-043.00GO:0034643establishment of mitochondrion localization, microtubule-mediated1.45E-043.00GO:0047477mitochondrion transport along microtubule1.45E-043.00GO:0047657negative regulation of viral entry into host cell2.09E-043.00GO:0045071negative regulation of viral genome replication2.13E-044.00GO:0045071negative regulation of viral genome replication2.13E-045.00GO:0022900electron transport chain2.28E-045.00	GO:0042775	mitochondrial ATP synthesis coupled electron transport	2.27E-05	5.00
GO:0046596regulation of viral entry into host cell3.68E-054.00GO:1902253regulation of intrinsic apoptotic signaling pathway by p53 class mediator4.23E-054.00KEGG:05016Huntington's disease4.28E-058.00KEGG:04932Non-alcoholic fatty liver disease (NAFLD)6.25E-057.00GO:0032642regulation of chemokine production1.03E-045.00GO:0022904respiratory electron transport chain1.43E-045.00GO:0032662chemokine production1.43E-045.00GO:0032602chemokine production1.43E-043.00GO:0032603establishment of mitochondrion localization, microtubule-mediated1.45E-043.00GO:0047497mitochondrion transport along microtubule1.45E-043.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0045071negative regulation of viral genome replication2.13E-044.00GO:0022909electron transport chain2.28E-045.00	GO:0006364	rRNA processing	3.05E-05	8.00
GO:1902253regulation of intrinsic apoptotic signaling pathway by p53 class mediator4.23E-054.00KEGG:05016Huntington's disease4.28E-058.00KEGG:04932Non-alcoholic fatty liver disease (NAFLD)6.25E-057.00GO:0032642regulation of chemokine production1.03E-045.00GO:0022904respiratory electron transport chain1.43E-045.00GO:0032602chemokine production1.43E-045.00GO:0032603establishment of mitochondrion localization, microtubule-mediated1.45E-043.00GO:0047497mitochondrion transport along microtubule1.82E-043.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0045624positive regulation of viral genome replication2.13E-044.00GO:0045071negative regulation of viral genome replication2.28E-045.00	GO:0042773	ATP synthesis coupled electron transport	3.27E-05	5.00
KEGG:05016Huntington's disease4.28E-058.00KEGG:04932Non-alcoholic fatty liver disease (NAFLD)6.25E-057.00GO:0032642regulation of chemokine production1.03E-045.00GO:0022904respiratory electron transport chain1.43E-045.00GO:0032602chemokine production1.43E-045.00GO:0032602chemokine production1.43E-045.00GO:0034643establishment of mitochondrion localization, microtubule-mediated1.45E-043.00GO:0047497mitochondrion transport along microtubule1.45E-043.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0045624positive regulation of viral genome replication2.13E-044.00GO:0022900electron transport chain5.003.00	GO:0046596	regulation of viral entry into host cell	3.68E-05	4.00
KEGG:04932Non-alcoholic fatty liver disease (NAFLD)6.25E-057.00GO:0032642regulation of chemokine production1.03E-045.00GO:0022904respiratory electron transport chain1.43E-045.00GO:0032602chemokine production1.43E-045.00GO:0032603establishment of mitochondrion localization, microtubule-mediated1.45E-043.00GO:0047497mitochondrion transport along microtubule1.45E-043.00GO:006119oxidative phosphorylation1.82E-045.00GO:0045697negative regulation of viral entry into host cell2.09E-043.00GO:0045071negative regulation of viral genome replication2.13E-044.00GO:0022900electron transport chain5.004.00	GO:1902253	regulation of intrinsic apoptotic signaling pathway by p53 class mediator	4.23E-05	4.00
GO:0032642regulation of chemokine production1.03E-045.00GO:0022904respiratory electron transport chain1.43E-045.00GO:0032602chemokine production1.43E-045.00GO:0034643establishment of mitochondrion localization, microtubule-mediated1.45E-043.00GO:0047497mitochondrion transport along microtubule1.45E-043.00GO:006119oxidative phosphorylation1.82E-045.00GO:0045697negative regulation of viral entry into host cell2.09E-043.00GO:0045624positive regulation of viral genome replication2.13E-044.00GO:0022900electron transport chain5.004.00	KEGG:05016	Huntington's disease	4.28E-05	8.00
GO:0022904respiratory electron transport chain1.43E-045.00GO:0032602chemokine production1.43E-045.00GO:0034643establishment of mitochondrion localization, microtubule-mediated1.45E-043.00GO:0047497mitochondrion transport along microtubule1.45E-043.00GO:0006119oxidative phosphorylation1.82E-045.00GO:0045597negative regulation of viral entry into host cell2.09E-043.00GO:0045624positive regulation of T-helper cell differentiation2.09E-043.00GO:0045071negative regulation of viral genome replication2.13E-044.00GO:0022900electron transport chain5.005.00	KEGG:04932	Non-alcoholic fatty liver disease (NAFLD)	6.25E-05	7.00
GO:0032602chemokine production1.43E-045.00GO:0034643establishment of mitochondrion localization, microtubule-mediated1.45E-043.00GO:0047497mitochondrion transport along microtubule1.45E-043.00GO:0006119oxidative phosphorylation1.82E-045.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0045624positive regulation of T-helper cell differentiation2.09E-043.00GO:0045071negative regulation of viral genome replication2.13E-044.00GO:0022900electron transport chain5.001.228E-045.00	GO:0032642	regulation of chemokine production	1.03E-04	5.00
GO:0034643establishment of mitochondrion localization, microtubule-mediated1.45E-043.00GO:0047497mitochondrion transport along microtubule1.45E-043.00GO:0006119oxidative phosphorylation1.82E-045.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0045624positive regulation of T-helper cell differentiation2.09E-043.00GO:0045071negative regulation of viral genome replication2.13E-044.00GO:0022900electron transport chain5.001.00	GO:0022904	respiratory electron transport chain	1.43E-04	5.00
GO:0047497mitochondrion transport along microtubule1.45E-043.00GO:0006119oxidative phosphorylation1.82E-045.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0045624positive regulation of T-helper cell differentiation2.09E-043.00GO:0045071negative regulation of viral genome replication2.13E-044.00GO:0022900electron transport chain5.00	GO:0032602	chemokine production	1.43E-04	5.00
GO:0006119oxidative phosphorylation1.82E-045.00GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0045624positive regulation of T-helper cell differentiation2.09E-043.00GO:0045071negative regulation of viral genome replication2.13E-044.00GO:0022900electron transport chain2.28E-045.00	GO:0034643	establishment of mitochondrion localization, microtubule-mediated	1.45E-04	3.00
GO:0046597negative regulation of viral entry into host cell2.09E-043.00GO:0045624positive regulation of T-helper cell differentiation2.09E-043.00GO:0045071negative regulation of viral genome replication2.13E-044.00GO:0022900electron transport chain2.28E-045.00	GO:0047497	mitochondrion transport along microtubule	1.45E-04	3.00
GO:0045624positive regulation of T-helper cell differentiation2.09E-043.00GO:0045071negative regulation of viral genome replication2.13E-044.00GO:0022900electron transport chain2.28E-045.00	GO:0006119	oxidative phosphorylation	1.82E-04	5.00
GO:0045071negative regulation of viral genome replication2.13E-044.00GO:0022900electron transport chain2.28E-045.00	GO:0046597	negative regulation of viral entry into host cell	2.09E-04	3.00
GO:0022900 electron transport chain 2.28E-04 5.00	GO:0045624	positive regulation of T-helper cell differentiation	2.09E-04	3.00
	GO:0045071	negative regulation of viral genome replication	2.13E-04	4.00
GO:0051654 establishment of mitochondrion localization 2.46E-04 3.00	GO:0022900	electron transport chain	2.28E-04	5.00
	GO:0051654	establishment of mitochondrion localization	2.46E-04	3.00

Table S4 Gene ontology (GO) analysis of GO: biological processes and KEGG pathway

GO:0002699	positive regulation of immune effector process	2.52E-04	7.00
KEGG:00190	Oxidative phosphorylation	2.56E-04	6.00
GO:0072332	intrinsic apoptotic signaling pathway by p53 class mediator	2.69E-04	5.00
GO:0035456	response to interferon-beta	2.74E-04	4.00
GO:0030490	maturation of SSU-rRNA	3.46E-04	4.00
GO:0032722	positive regulation of chemokine production	3.46E-04	4.00
GO:0035455	response to interferon-alpha	3.86E-04	3.00
GO:0002293	alpha-beta T cell differentiation involved in immune response	4.02E-04	4.00
GO:0022408	negative regulation of cell-cell adhesion	4.05E-04	6.00
GO:0046632	alpha-beta T cell differentiation	4.25E-04	5.00
GO:0002287	alpha-beta T cell activation involved in immune response	4.32E-04	4.00
GO:0002286	T cell activation involved in immune response	5.12E-04	5.00

G0:0006996 organelle organization 4.71E-18 124.00 G0:1903047 mitotic cell cycle process 1.67E-14 45.00 G0:0051276 chromosome organization 6.70E-14 55.00 G0:0022402 cell cycle process 1.02E-13 56.00 G0:0002280 nuclear division 1.13E-12 38.00 G0:000278 mitotic cell cycle 1.38E-12 45.00 G0:000276 mitotic nuclear division 3.09E-12 32.00 G0:000275 organelle fission 1.00E-11 38.00 G0:000276 mitotic nuclear division 3.09E-12 32.00 G0:0002750 chromosome segregation 5.82E-09 22.00 G0:000276 reinomosome segregation 5.82E-09 22.00 G0:000271 negative regulation of nucleobase-contatining compound metabolic process 3.61E-08 <th>ID</th> <th>GO term (downregulated)</th> <th>Term <i>p</i> value</th> <th>Nr. genes</th>	ID	GO term (downregulated)	Term <i>p</i> value	Nr. genes
G0:0051276 chromosome organization 6.70E-14 55.00 G0:0022402 cell cycle process 1.02E-13 55.00 G0:0007049 cell cycle 1.77E-13 66.00 G0:0007040 nuclear division 1.13E-12 38.00 G0:0000228 nuclear division 1.14E-12 37.00 G0:00007067 mitotic cell cycle 1.35E-12 45.00 G0:00070767 mitotic nuclear division 3.09E-12 32.00 G0:0007067 mitotic nuclear division 3.09E-12 32.00 G0:0007067 mitotic nuclear division 3.09E-12 32.00 G0:0007058 organelle fission 1.00E-11 38.00 G0:0007059 Inomosome segregation 5.82E-09 22.00 KEGG:04110 Cell cycle 1.79E-08 14.00 G0:0007031 regative regulation of nucleobase-containing compound metabolic process 2.21E-08 53.00 G0:0007031 lelomere organization 7.05E-08 13.00 G0:0007051 spindle organization 7.05E-08 13.00	GO:0006996	organelle organization	4.71E-18	124.00
GO:0022402 cell cycle process 1.02E-13 55.00 GO:0007049 cell cycle 1.77E-13 66.00 GO:000280 nuclear division 1.13E-12 38.00 GO:0002761 cell division 1.14E-12 37.00 GO:0002763 mitotic cell cycle 1.35E-12 45.00 GO:0002764 mitotic cell cycle 3.09E-12 32.00 GO:0002765 organelle fission 1.00E-11 38.00 GO:0002765 organelle fission 1.00E-11 38.00 GO:0002765 pagnelle fission 1.00E-11 38.00 GO:0002765 regulation of DNA metabolic process 4.23E-11 44.00 GO:0007059 chromosome segregation 5.82E-09 22.00 KEGG:04110 Cell cycle 1.79E-08 14.00 GO:000728 negative regulation of nitrogen compound metabolic process 3.61E-08 53.00 GO:000729 lelomere maintenance 6.36E-08 13.00 1.00E-11 3.00 GO:000728 kelomere organization 7.05E-08 13	GO:1903047	mitotic cell cycle process	1.67E-14	45.00
GO.0007049 cell cycle 1.77E-13 66.00 GO.000280 nuclear division 1.13E-12 38.00 GO.000210 cell division 1.14E-12 37.00 GO.000278 mitotic cell cycle 1.35E-12 45.00 GO.0002767 mitotic nuclear division 3.09E-12 32.00 GO.0002768 organelle fission 1.00E-11 38.00 GO.0002629 DNA metabolic process 4.23E-11 44.00 GO.0007050 chromosome segregation 5.82E-09 22.00 GO.0007050 chromosome segregation 5.82E-09 22.00 KEGG:04110 Cell cycle 1.79E-08 14.00 GO.000753 negative regulation of nitrogen compound metabolic process 2.21E-08 57.00 GO.0007531 leomere maintenance 6.36E-08 13.00 13.00 GO.000723 telomere organization 7.05E-08 13.00 13.00 13.00 13.00 13.00 13.00 13.00 13.00 13.00 13.00 13.00 13.00 13.00	GO:0051276	chromosome organization	6.70E-14	55.00
GO:000280 nuclear division 1.13E-12 38.00 GO:0051301 cell division 1.14E-12 37.00 GO:000278 mitotic cell cycle 1.35E-12 45.00 GO:0007067 mitotic nuclear division 3.09E-12 32.00 GO:0006259 DNA metabolic process 4.23E-11 44.00 GO:0007059 circonsome segregation 5.82E-09 22.00 GO:0007059 chromosome segregation 5.82E-09 22.00 GO:0007172 negative regulation of nitrogen compound metabolic process 2.21E-08 57.00 GO:000723 telomere maintenance 6.36E-08 13.00 GO:000723 telomere organization 7.05E-08 13.00 GO:0007051 spindle organization 7.38E-07 18.00 GO:0007051 spindle organization 1.38E-07 18.00 GO:0007053 negative regulation of macromolecule biosynthetic process 1.64E-07 52.00 GO:0007051 spindle organization 1.38E-07 18.00 GO:0007053 negative regulation of macromolecule biosynthetic p	GO:0022402	cell cycle process	1.02E-13	55.00
GO:0051301cell division1.14E-1237.00GO:0000278mitotic cell cycle1.35E-1245.00GO:0007067mitotic nuclear division3.09E-1232.00GO:0042828organelle fission1.00E-1138.00GO:005259DNA metabolic process4.23E-1144.00GO:007069regulation of DNA metabolic process9.86E-1026.00GO:007059chromosome segregation5.82E-0922.00KEG:04110Cell cycle1.79E-0814.00GO:0051172negative regulation of nitrogen compound metabolic process3.61E-0853.00GO:000703telomere maintenance6.36E-0813.00GO:000704telomere organization7.05E-0813.00GO:0007051spindle organization1.11E-0714.00GO:001052negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:0010551negative regulation of cellular macromolecule biosynthetic process1.69E-0750.00GO:0010551negative regulation of macromolecule biosynthetic process1.69E-0750.00GO:001055negative regulation of necromolecule biosynthetic process1.69E-0750.00GO:001055negative regulation of macromolecule biosynthetic process1.99E-0774.00GO:001055negative regulation of macromolecule metabolic process1.99E-0774.00GO:001055negative regulation of macromolecule metabolic process1.99E-0774.00GO:001055negative regulation of biosynthetic process <t< td=""><td>GO:0007049</td><td>cell cycle</td><td>1.77E-13</td><td>66.00</td></t<>	GO:0007049	cell cycle	1.77E-13	66.00
GO:0000278 mitotic cell cycle 1.35E-12 45.00 GO:000707 mitotic nuclear division 3.09E-12 32.00 GO:000708 organelle fission 1.00E-11 38.00 GO:0006259 DNA metabolic process 4.23E-11 44.00 GO:0007050 regulation of DNA metabolic process 9.86E-10 26.00 GO:0007059 chromosome segregation 5.82E-09 22.00 KEGG:04110 Cell cycle 1.79E-08 14.00 GO:00051172 negative regulation of nitrogen compound metabolic process 2.21E-08 57.00 GO:0007031 telomere maintenance 6.36E-08 13.00 GO:000723 telomere organization 7.8E-08 13.00 GO:000724 DNA-dependent DNA replication 7.8E-08 13.00 GO:000725 spindle organization 1.31E-07 14.00 GO:000726 DNA-dependent DNA replication 1.38E-07 52.00 GO:000726 DNA-replication of macromolecule biosynthetic process 1.64E-07 52.00 GO:0000526 DNA replication of macromolecu	GO:0000280	nuclear division	1.13E-12	38.00
GO:0007067 mitotic nuclear division 3.09E-12 32.00 GO:0048285 organelle fission 1.00E-11 38.00 GO:0006259 DNA metabolic process 4.23E-11 44.00 GO:0007050 regulation of DNA metabolic process 9.86E-10 26.00 GO:0007059 chromosome segregation 5.82E-09 22.00 KEGG:04110 Cell cycle 1.79E-08 14.00 GO:0051172 negative regulation of nitrogen compound metabolic process 2.21E-08 57.00 GO:000703 telomere maintenance 6.36E-08 13.00 GO:000723 telomere organization 7.05E-08 13.00 GO:000724 pipledendent DNA replication 7.81E-08 13.00 GO:000725 pipled organization 1.11E-07 14.00 GO:000726 DNA replication of macromolecule biosynthetic process 1.69E-07 52.00 GO:0010558 negative regulation of cellular macromolecule biosynthetic process 1.69E-07 50.00 GO:0010550 negative regulation of macromolecule metabolic process 1.69E-07 50.00 <	GO:0051301	cell division	1.14E-12	37.00
GO:0048285organelle fission1.00E-1138.00GO:006259DNA metabolic process4.23E-1144.00GO:0051052regulation of DNA metabolic process9.86E-1026.00GO:0007059chromosome segregation5.82E-0922.00KEGG:04110Cell cycle1.79E-0814.00GO:0051172negative regulation of nitrogen compound metabolic process3.61E-0853.00GO:0045934negative regulation of nucleobase-containing compound metabolic process3.61E-0853.00GO:000723telomere organization7.05E-0813.00GO:0006261DNA-dependent DNA replication7.81E-0813.00GO:000705spindle organization1.11E-0714.00GO:000705negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:001058negative regulation of macromolecule metabolic process1.69E-0750.00GO:001050negative regulation of macromolecule metabolic process1.69E-0774.00GO:0010605negative regulation of biosynthetic process1.99E-0774.00GO:000980negative regulation of biosynthetic process1.99E-0754.00	GO:0000278	mitotic cell cycle	1.35E-12	45.00
GO:0006259 DNA metabolic process 4.23E-11 44.00 GO:0051052 regulation of DNA metabolic process 9.86E-10 26.00 GO:0007059 chromosome segregation 5.82E-09 22.00 KEGG:04110 Cell cycle 1.79E-08 14.00 GO:005172 negative regulation of nitrogen compound metabolic process 2.21E-08 57.00 GO:0045934 negative regulation of nucleobase-containing compound metabolic process 3.61E-08 53.00 GO:000723 telomere maintenance 6.36E-08 13.00 GO:000723 telomere organization 7.05E-08 13.00 GO:000724 psindle organization 7.81E-08 13.00 GO:0007051 spindle organization 1.11E-07 14.00 GO:0007052 cagative regulation of macromolecule biosynthetic process 1.64E-07 52.00 GO:0010558 negative regulation of macromolecule biosynthetic process 1.69E-07 50.00 GO:001055 negative regulation of macromolecule metabolic process 1.99E-07 74.00 GO:00008900 negative regulation of biosynthetic process	GO:0007067	mitotic nuclear division	3.09E-12	32.00
G0:0051052 regulation of DNA metabolic process 9.86E-10 26.00 G0:0007059 chromosome segregation 5.82E-09 22.00 KEGG:04110 Cell cycle 1.79E-08 14.00 G0:0051172 negative regulation of nitrogen compound metabolic process 2.21E-08 57.00 G0:0045934 negative regulation of nucleobase-containing compound metabolic process 3.61E-08 53.00 G0:000723 telomere maintenance 6.36E-08 13.00 G0:0006261 DNA-dependent DNA replication 7.05E-08 13.00 G0:0007051 spindle organization 1.11E-07 14.00 G0:0006260 DNA replication of macromolecule biosynthetic process 1.64E-07 52.00 G0:0010558 negative regulation of cellular macromolecule biosynthetic process 1.69E-07 50.00 G0:0010558 negative regulation of macromolecule metabolic process 1.69E-07 50.00 G0:0010655 negative regulation of macromolecule metabolic process 1.99E-07 74.00 G0:0009890 negative regulation of biosynthetic process 1.99E-07 54.00	GO:0048285	organelle fission	1.00E-11	38.00
GO:0007059chromosome segregation5.82E-0922.00KEGG:04110Cell cycle1.79E-0814.00GO:0051172negative regulation of nitrogen compound metabolic process2.21E-0857.00GO:0045934negative regulation of nucleobase-containing compound metabolic process3.61E-0853.00GO:000723telomere maintenance6.36E-0813.00GO:0032200telomere organization7.05E-0813.00GO:0006261DNA-dependent DNA replication7.81E-0813.00GO:0007051spindle organization1.11E-0714.00GO:0010558negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:0010558negative regulation of macromolecule biosynthetic process1.69E-0750.00GO:0010605negative regulation of macromolecule biosynthetic process1.99E-0774.00GO:0009890negative regulation of biosynthetic process2.11E-0754.00	GO:0006259	DNA metabolic process	4.23E-11	44.00
KEGG:04110Cell cycle1.79E-0814.00GO:0051172negative regulation of nitrogen compound metabolic process2.21E-0857.00GO:0045934negative regulation of nucleobase-containing compound metabolic process3.61E-0853.00GO:000723telomere maintenance6.36E-0813.00GO:0032200telomere organization7.05E-0813.00GO:0006261DNA-dependent DNA replication7.81E-0813.00GO:0007051spindle organization1.11E-0714.00GO:0007055negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:0010558negative regulation of cellular macromolecule biosynthetic process1.69E-0750.00GO:0010655negative regulation of macromolecule biosynthetic process1.99E-0774.00GO:0009890negative regulation of biosynthetic process2.11E-0754.00	GO:0051052	regulation of DNA metabolic process	9.86E-10	26.00
GO:0051172negative regulation of nitrogen compound metabolic process2.21E-0857.00GO:0045934negative regulation of nucleobase-containing compound metabolic process3.61E-0853.00GO:0000723telomere maintenance6.36E-0813.00GO:0032200telomere organization7.05E-0813.00GO:0006261DNA-dependent DNA replication7.81E-0813.00GO:0007051spindle organization1.11E-0714.00GO:0006260DNA replication1.38E-0718.00GO:0010558negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:0010655negative regulation of macromolecule biosynthetic process1.99E-0774.00GO:0010650negative regulation of biosynthetic process2.11E-0754.00	GO:0007059	chromosome segregation	5.82E-09	22.00
GO:0045934negative regulation of nucleobase-containing compound metabolic process3.61E-0853.00GO:000723telomere maintenance6.36E-0813.00GO:0032200telomere organization7.05E-0813.00GO:0006261DNA-dependent DNA replication7.81E-0813.00GO:0007051spindle organization1.11E-0714.00GO:0006260DNA replication1.38E-0718.00GO:0010558negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:0010655negative regulation of macromolecule biosynthetic process1.69E-0774.00GO:0010655negative regulation of macromolecule process1.99E-0774.00GO:0009890negative regulation of biosynthetic process2.11E-0754.00	KEGG:04110	Cell cycle	1.79E-08	14.00
GO:0000723telomere maintenance6.36E-0813.00GO:0032200telomere organization7.05E-0813.00GO:0006261DNA-dependent DNA replication7.81E-0813.00GO:0007051spindle organization1.11E-0714.00GO:0006260DNA replication1.38E-0718.00GO:0010558negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:0010655negative regulation of cellular macromolecule biosynthetic process1.99E-0774.00GO:0010655negative regulation of biosynthetic process1.99E-0774.00GO:0010655negative regulation of biosynthetic process2.11E-0754.00	GO:0051172	negative regulation of nitrogen compound metabolic process	2.21E-08	57.00
GO:0032200telomere organization7.05E-0813.00GO:0006261DNA-dependent DNA replication7.81E-0813.00GO:0007051spindle organization1.11E-0714.00GO:0006260DNA replication1.38E-0718.00GO:0010558negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:2000113negative regulation of cellular macromolecule biosynthetic process1.69E-0750.00GO:0010655negative regulation of macromolecule process1.99E-0774.00GO:0010655negative regulation of biosynthetic process2.11E-0754.00	GO:0045934	negative regulation of nucleobase-containing compound metabolic process	3.61E-08	53.00
GO:0006261DNA-dependent DNA replication7.81E-0813.00GO:0007051spindle organization1.11E-0714.00GO:0006260DNA replication1.38E-0718.00GO:0010558negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:2000113negative regulation of cellular macromolecule biosynthetic process1.69E-0750.00GO:0010655negative regulation of macromolecule metabolic process1.99E-0774.00GO:0009890negative regulation of biosynthetic process2.11E-0754.00	GO:0000723	telomere maintenance	6.36E-08	13.00
GO:0007051spindle organization1.11E-0714.00GO:0006260DNA replication1.38E-0718.00GO:0010558negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:2000113negative regulation of cellular macromolecule biosynthetic process1.69E-0750.00GO:0010605negative regulation of macromolecule metabolic process1.99E-0774.00GO:0009890negative regulation of biosynthetic process2.11E-0754.00	GO:0032200	telomere organization	7.05E-08	13.00
GO:0006260DNA replication1.38E-0718.00GO:0010558negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:2000113negative regulation of cellular macromolecule biosynthetic process1.69E-0750.00GO:0010605negative regulation of macromolecule metabolic process1.99E-0774.00GO:0009890negative regulation of biosynthetic process2.11E-0754.00	GO:0006261	DNA-dependent DNA replication	7.81E-08	13.00
GO:0010558negative regulation of macromolecule biosynthetic process1.64E-0752.00GO:2000113negative regulation of cellular macromolecule biosynthetic process1.69E-0750.00GO:0010605negative regulation of macromolecule metabolic process1.99E-0774.00GO:0009890negative regulation of biosynthetic process2.11E-0754.00	GO:0007051	spindle organization	1.11E-07	14.00
GO:2000113negative regulation of cellular macromolecule biosynthetic process1.69E-0750.00GO:0010605negative regulation of macromolecule metabolic process1.99E-0774.00GO:0009890negative regulation of biosynthetic process2.11E-0754.00	GO:0006260	DNA replication	1.38E-07	18.00
GO:0010605negative regulation of macromolecule metabolic process1.99E-0774.00GO:0009890negative regulation of biosynthetic process2.11E-0754.00	GO:0010558	negative regulation of macromolecule biosynthetic process	1.64E-07	52.00
GO:0009890negative regulation of biosynthetic process2.11E-0754.00	GO:2000113	negative regulation of cellular macromolecule biosynthetic process	1.69E-07	50.00
	GO:0010605	negative regulation of macromolecule metabolic process	1.99E-07	74.00
GO:0006281 DNA repair 2.41E-07 24.00	GO:0009890	negative regulation of biosynthetic process	2.11E-07	54.00
	GO:0006281	DNA repair	2.41E-07	24.00

GO:0000070	mitotic sister chromatid segregation	2.46E-07	13.00
GO:0031327	negative regulation of cellular biosynthetic process	3.07E-07	53.00
GO:0031324	negative regulation of cellular metabolic process	3.13E-07	74.00
GO:0000226	microtubule cytoskeleton organization	4.19E-07	25.00
GO:0060249	anatomical structure homeostasis	4.33E-07	21.00
GO:0000819	sister chromatid segregation	4.45E-07	14.00
GO:0098813	nuclear chromosome segregation	4.87E-07	17.00
GO:0033044	regulation of chromosome organization	6.25E-07	19.00
GO:0033554	cellular response to stress	6.92E-07	54.00
GO:0071103	DNA conformation change	1.81E-06	15.00
GO:0051726	regulation of cell cycle	1.89E-06	35.00
GO:0071897	DNA biosynthetic process	2.64E-06	13.00
GO:0006302	double-strand break repair	2.71E-06	14.00
GO:0051054	positive regulation of DNA metabolic process	2.90E-06	15.00
GO:0051173	positive regulation of nitrogen compound metabolic process	3.11E-06	57.00
GO:0032210	regulation of telomere maintenance via telomerase	6.02E-06	7.00
GO:0051649	establishment of localization in cell	7.68E-06	54.00
GO:0044772	mitotic cell cycle phase transition	9.60E-06	18.00
GO:0046907	intracellular transport	1.08E-05	46.00
GO:0006974	cellular response to DNA damage stimulus	1.11E-05	28.00
GO:1902850	microtubule cytoskeleton organization involved in mitosis	1.34E-05	9.00
GO:0007052	mitotic spindle organization	1.34E-05	9.00
GO:0010564	regulation of cell cycle process	1.37E-05	23.00
GO:0051253	negative regulation of RNA metabolic process	1.39E-05	43.00
GO:0007346	regulation of mitotic cell cycle	1.49E-05	21.00
GO:0007010	cytoskeleton organization	1.53E-05	40.00
GO:1902679	negative regulation of RNA biosynthetic process	1.61E-05	42.00
GO:0010833	telomere maintenance via telomere lengthening	1.75E-05	8.00
GO:0034502	protein localization to chromosome	1.95E-05	8.00
GO:0007004	telomere maintenance via telomerase	2.20E-05	7.00
GO:0033043	regulation of organelle organization	2.28E-05	39.00
GO:1903507	negative regulation of nucleic acid-templated transcription	2.46E-05	41.00
GO:0090307	mitotic spindle assembly	2.50E-05	7.00
GO:1904356	regulation of telomere maintenance via telomere lengthening	2.50E-05	7.00
GO:0032204	regulation of telomere maintenance	2.66E-05	8.00
GO:0045935	positive regulation of nucleobase-containing compound metabolic process	2.72E-05	52.00
GO:0044770	cell cycle phase transition	2.76E-05	18.00
GO:0045892	negative regulation of transcription, DNA-templated	3.29E-05	40.00