

¹ Host Turkey B-cell Transcriptomics During THEV Infection
² Highlights Upregulated Cell Death and Breakdown Pathways
³ That May Mediate Immunosuppression

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16 **ABSTRACT**

17 INTRODUCTION

18 Turkey hemorrhagic enteritis virus (THEV), belonging to the family *Adenoviridae*, genus *Siadenovirus*, in-
19 fects turkeys, chickens, and pheasants (1, 2). Infecting its hosts via the feco-oral route, THEV causes
20 hemorrhagic enteritis (HE) in turkeys, a debilitating disease affecting predominantly 6-12-week-old turkey
21 pouls characterized by immunosuppression (IMS), depression, splenomegaly, intestinal lesions leading to
22 bloody droppings, and up to 80% mortality (3-6). The clinical disease usually persists in affected flocks for
23 about 7-10 days. However, secondary bacterial infections may extend the duration of illness and mortality
24 for an additional 2-3 weeks due to the immunosuppressive nature of the virus, exacerbating the economic
25 losses (5, 7). Low pathogenic (avirulent) strains of THEV have been isolated, which show subclinical in-
26 fections but retain the immunosuppressive effects. Since its isolation from a pheasant spleen, the Virginia
27 Avirulent Strain (VAS) has been used effectively as a live vaccine despite the immunosuppressive side-
28 effects, but the vaccinated birds are rendered more susceptible to opportunistic infections and death than
29 unvaccinated cohorts leading to significant economic losses (4, 5, 8-10).

30 It is well-established that THEV primarily infects and replicates in turkey B-cells of the bursa and spleen and
31 somewhat in macrophages, inducing apoptosis and necrosis. Consequently, a significant drop in number
32 of B-cells (specifically, IgM+ B-cells) and macrophages ensue along with increased T-cell counts with ab-
33 normal T-cell subpopulation (CD4+ and CD8+) ratios. The cell death seen in the B-cells and macrophages
34 is generally proposed as the major cause of THEV-induced IMS as both humoral and cell-mediated immu-
35 nity are impaired (5, 6, 8, 11). It is also thought that the virus replication in the spleen attracts T-cells and
36 peripheral blood macrophages to the spleen where the T-cells are activated by cytokines from activated
37 macrophages and vice versa. The activated T-cells undergo clonal expansion and secrete interferons: type
38 I (IFN- α and IFN- β) and type II (IFN- γ) as well as tumor necrosis factor (TNF) while activated macrophages
39 secrete interleukin 6 (IL-6), TNF, and nitric oxide (NO), an antiviral agent with immunosuppressive proper-
40 ties. The inflammatory cytokines released by T-cells and macrophages (e.g., TNF and IL-6) may also induce
41 apoptosis in bystander splenocytes, exacerbating the already numerous apoptotic and necrotic splenocytes,
42 culminating in IMS (8, 11) (see **Figure 1**). However, the precise molecular mechanisms of THEV-induced
43 IMS or pathways involved are poorly understood (6). Elucidating the specific mechanisms and pathways of
44 THEV-induced IMS is the most crucial step in THEV research as it will present a means of mitigating the
45 IMS.

46 Next generation sequencing (NGS) is a groundbreaking technology that has significantly enhanced our un-
47 derstanding of DNA and RNA structure and function and facilitated exceptional advancements in all domains
48 of biology and the Life Sciences (12). mRNA sequencing (RNA-seq), an NGS approach to transcriptomic

49 studies, is a versatile, high throughput, and cost-effective technology that allows a broad scan of the entire
50 transcriptome, thereby uncovering the active genes and molecular pathways and processes. This tech-
51 nology has been leveraged in an ever increasing number of studies to elucidate active cellular processes
52 under a wide range of treatment conditions, including the transcriptomics of viral infections (12–16). In
53 RNA-seq studies, differentially expressed genes (DEGs) identified under different experimental conditions
54 are key to unlocking the interesting biology or mechanism under study. Identified DEGs are typically used
55 for functional enrichment analysis in large curated knowledgebases which connect genes to specific bio-
56 logical processes, functions, and pathways such as gene ontology (GO) and Kyoto Encyclopedia of Genes
57 and Genomes (KEGG) pathways, shedding light on the biological question under study (17, 18).

58 To the best of our knowledge, no study has leveraged the wealth of information offered by RNA-seq to
59 elucidate the molecular mechanisms and pathways leading to THEV-induced IMS. To effectively counteract
60 the immunosuppressive effect of the vaccine, it is essential to unravel the host cell mechanisms/pathways
61 influenced by the virus to bring about IMS. In this study, we present the first transcriptomic profile of THEV-
62 infected cells using paired-end RNA-seq in a turkey B-cell line (MDTC-RP19), highlighting key host genes,
63 cellular/molecular processes and pathways affected during a THEV infection. We specifically focus on
64 cellular processes that would help in elucidating THEV-induced IMS. Our RNA-seq yielded 149 bp long high
65 quality (mean PHRED Score of 36) sequences from each end of cDNA fragments, which were mapped to
66 the genome of domestic turkey (*Meleagris gallopavo*).

67 **RESULTS**

68 **Sequencing Results**

69 To identify the host transcriptome profile during THEV infection, MDTC-RP19 cells were THEV-infected or
70 mock-infected in triplicates or duplicates, respectively, and harvested at 4-, 12-, 24-, and 72-hours post in-
71 fection (hpi). mRNAs extracted from mock- or THEV-infected cells were sequenced on the Illumina platform,
72 yielding a total of **776.1** million raw reads (149 bp in length) across all samples (statistics for the sequencing
73 reads obtained from each RNA library are presented in **Table 1**). After trimming off low-quality reads, the
74 remaining **742.8** million total paired-end trimmed reads (approximately, **34.7-47.9** million reads per sample)
75 were mapped to the genome of *Meleagris gallopavo* obtained from the National Center for Biotechnology
76 Information (NCBI). The percentage of reads mapping to the host genome across all samples ranged from
77 **32.4-89.2%**. Although our sequencing reads have excellent quality scores at all time points (see **Table 1**),
78 the DEGs identified at 4- and 72-hpi did not yield any results in the functional enrichment analyses (i.e.,
79 GO term and KEGG pathway analysis); hence, they were excluded from all subsequent analyses. In the
80 remaining samples from 12- and 24-hpi, a high correlation was seen between biological replicates (**Figure**
81 **2A and B**).

82 **DEGs of THEV-infected Versus Mock-infected Cells**

83 Gene expression levels were estimated with the StringTie software (19) in Fragments per kilobase of tran-
84 script per million (FPKM) units. The analysis of DEGs was performed with the DESeq2 R package (20)
85 which employs negative binomial distribution model for read count comparisons. Using a P_{adjusted} -value
86 cutoff ≤ 0.05 as the inclusion criteria, a total of **2,343** and **3,295** genes were identified as differentially
87 expressed at 12-hpi and 24-hpi, respectively. ~~The DEG analyses results at 12 and 24 hpi are presented~~
88 in **Supplementary Tables 1 and 2**, respectively. At 12-hpi, **1,079** genes were upregulated and **1,264**
89 genes downregulated, whereas **1,512** genes were upregulated and **1,783** genes downregulated at 24-hpi
90 (**Figure 2C**, and **Figure 3A-C**). The log₂fold-change(FC) values at 12-hpi ranged between **-1.4** and **+1.7**
91 for **TMEM156** (Transmembrane Protein 156) and **LIPG** (Lipase G), respectively. At 24-hpi, the log₂FC val-
92 ues ranged between **-2.0** and **+2.6** for **C1QTNF12** (C1q And TNF Related 12) and **KCNG1** (Potassium
93 Voltage-Gated Channel Modifier Subfamily G Member 1), respectively.

94 **Functional Enrichment Analyses (GO, KEGG pathway, and interaction network analyses)**

95 Gene ontology (GO) enrichment analysis was performed for 12- and 24-hpi DEGs with the DAVID (Database
96 for Annotation, Visualization and Integrated Discovery; version 2021) online resource (21) and the gprofiler2
97 R package – version **0.2.3** (22), which output results in three GO categories – cellular components (CP),

98 biological processes (BP), and molecular functions (MF). Results with P_{adjusted} -value ≤ 0.05 were considered functionally enriched. The GO enrichment analyses results at 12-hpi and 24-hpi showed significant intersections among all three GO categories. At both time points, cellular breakdown processes were upregulated while cellular maintenance processes and structures were downregulated in all three GO categories (Table 2A-B and Table 3A-B).

103 For upregulated DEGs at 12-hpi, GO terms annotated under the BP category broadly cluster into: apoptosis
104 and autophagy, cellular metabolism (catabolic processes), sterol biosynthesis, response to stimuli, and
105 protein processing (Figure 4A and Table 2A). Under the CC category, the GO terms relate primarily with
106 cytoplasmic vacuolation while the GO terms under the MF category broadly fit under protein binding and
107 kinase activity (Table 2A). For 12-hpi downregulated DEGs, the GO terms in BP category generally fall
108 under: translation, protein biosynthesis and folding, ribosome biogenesis, nitrogen compound metabolism,
109 nucleic acid synthesis, repair, metabolism, processing, and replication; and energy metabolism. Also,
110 immunoglobulin production and isotype switching was downregulated (Figure 4C and Table 2B). As for
111 the CC category GO terms, they broadly group into: ribosome, mitochondria, respirosome, nucleus, and
112 spliceosome while the MF category GO terms generally belong to: translation regulator activity, protein
113 folding chaperone, catalytic activity (acting on a nucleic acids), and ATP hydrolysis activity (Table 2B).

114 At 24-hpi, the GO terms under the BP GO category for the upregulated DEGs are connected with: apoptosis
115 and autophagy, lipid and sterol biosynthesis, catabolic process, protein ubiquitination and proteolysis,
116 cell signalling, and cell metabolism. Additionally, host defense response and genes that negatively regulate
117 cytokine production were upregulated (Figure 4B and Table 3A). The GO terms of the CC category,
118 similar to those identified at 12-hpi, are also related with cytoplasmic vacuolation and the lysosome. The
119 MF category GO terms group into: protein ubiquitination activity, kinase and acyltransferase activity, and
120 macromolecule binding activity (Table 3A). The GO terms for the downregulated DEGs are markedly similar
121 to those at 12-hpi in all three GO categories. The BP category GO terms broadly group into: translation,
122 peptide biosynthesis and folding, ribosome biogenesis, aerobic respiration and ATP synthesis, and cell cycle
123 process and nucleic acid replication and processing (Figure 4D and Table 3B). The GO terms of the
124 CC category group under: ribosome, mitochondrion, nucleus and chromosomes while the MF category GO
125 terms group into: structural constituent of ribosome and translation regulator activity, catalytic activity acting
126 on a nucleic acid and nucleic acid binding, aminoacyl-tRNA ligase activity, and NAD binding (Table 3B).

127 KEGG pathway analysis on the DEGs was also performed using both the gprofiler2 R package (22) and
128 the DAVID online resource. Both analysis resources gave similar results but the results from DAVID (Table
129 4A) includes more information than the gprofiler2 results (Table 4B). The KEGG pathway analysis was

130 congruent with the GO results, revealing that generally, cell maintenance and upkeep pathways were down-
131 regulated while cell death and breakdown pathways were upregulated. Cell maintenance pathways such
132 as DNA replication and repair, ribosome biogenesis, spliceosome, and oxidative phosphorylation were
133 downregulated at 12-hpi. Similar pathways were downregulated at 24-hpi. Pathways such as: autophagy,
134 response to virus (Influenza A), and steroid biosynthesis were upregulated at 12-hpi similar to 24-hpi, where
135 pathways such as: autophagy, ubiquitin-mediated proteolysis, lysosome, protein processing in endoplasmic
136 reticulum, and steroid biosynthesis were upregulated.

137 It is well-established that THEV induces cell death (apoptosis and necrosis) in infected B-cells, which is
138 linked to THEV-induced IMS (8, 11, 23). Hence, we are particularly interested in cellular processes and
139 pathways associated with cell death and pathways that may affect the survivability of the host B-cells,
140 thereby accounting for THEV-induced IMS. We highlight the upregulated cell death (apoptosis and au-
141 topagy) pathways and responses to stimuli (especially the ubiquitin-dependent endoplasmic reticulum
142 [ER]-related protein degradation) pathways identified by our GO and KEGG analyses as the likely key as-
143 pects of THEV-host cell interaction relevant to THEV-induced IMS.

144 **Cell Death and Breakdown Pathways Upregulated by THEV**

145 Many virus families, including adenoviruses, herpesviruses, poxviruses, baculoviruses, parvoviruses, retro-
146 viruses, rhabdoviruses, paramyxoviruses, orthomyxoviruses, togaviruses, and picornaviruses are known
147 to trigger apoptosis in infected host cells either by a direct action of a viral protein or due to the host antivi-
148 ral response (24–26). The Mastadenovirus family possess the protein, E1B-19K, used to inhibit host cell
149 apoptosis long enough to complete their replication cycle (24, 26, 27). However, no such protein is known
150 in THEV. A recent paper showed several novel transcripts and open reading frames (ORFs) in the genome
151 of THEV which may offer similar anti-apoptotic functions but the functions of these novel ORFs are yet
152 to be studied (28). Our data show that apoptotic and autophagic pathways are upregulated during THEV
153 infection, supporting previous findings of apoptosis and necrosis of THEV-infected cells (8, 11, 23). For
154 example, several proapoptotic members of the BCL2 (B-cell lymphoma 2) protein family such as: BCL2 an-
155 tagonist/killer 1 (BAK1), BCL2 interacting protein 3 like (BNIP3L), BCL2 interacting protein 3 (BNIP3), and
156 Bcl2 modifying factor (BMF) were upregulated. Additionally, Fas cell surface death receptor (FAS), Fas as-
157 sociated via death domain (FADD), MAP kinase-activating death domain (MADD), programmed cell death
158 4(PDCD4), RB1 inducible coiled-coil 1 (RB1CC1), activating transcription factor 4 (ATF4), receptor interact-
159 ing serine/threonine kinase 1 (RIPK1), tumor necrosis factor receptor superfamily member 1B (TNFRSF1B),
160 pro-apoptotic WT1 regulator (PAWR), and apoptotic peptidase activating factor 1 (APAF1), which are po-
161 tent proapoptotic factors were upregulated. Interestingly, both the intrinsic (BAK1, BNIP3L, BNIP3, BMF,

RB1CC1, ATF4, PDCD4, and APAF1) and extrinsic (FAS, FADD, TNFRSF1B, MADD, and RIPK1) apoptotic pathways were represented. Conversely, we noted that, several anti-apoptotic proteins such as: BCL2 apoptosis regulator (BCL2), BCL2 interacting protein 2 (BNIP2; interacts directly with adenovirus E1B-19K protein), BCL2 related protein A1 (BCL2A1), and apoptosis inhibitor 5 (API5) were also upregulated. Thus, apoptosis and its regulation pathways are clearly upregulated; this likely highlights the host-virus tug-of-war and underscores the ability of adenoviruses to trigger both apoptotic and anti-apoptotic pathways as seen in Mastadenoviruses. Moreover, several genes associated with autophagy such as: TNF receptor associated factor 6 (TRAF6), autophagy related 9A (ATG9A), unc-51 like autophagy activating kinase 2 (ULK2), and autophagy related 4B cysteine peptidase (ATG4B) were upregulated.

We also found several essential cell maintenance processes whose downregulation can trigger apoptosis. For instance, severe DNA damage is a known mechanism of apoptosis induction, which is called DNA damage-dependent apoptosis (29). Repression of RNA and protein synthesis are also strongly associated with apoptosis (30). Several processes related nucleic acid (DNA and RNA) synthesis, maintenance, and repair such as: nucleotide biosynthesis and metabolism, double strand break repair, DNA excision repair, RNA biosynthesis, RNA processing, DNA replication, mitotic cell cycle process, protein-RNA complex organization, and DNA damage response were downregulated. Some notable genes identified include: DNA ligase 1 (LIG1), X-ray repair cross complementing 1 (XRCC1), cyclin dependent kinase 1 and 2 (CDK1, CDK2), checkpoint kinase 1 (CHEK1), 8-oxoguanine DNA glycosylase (OGG1), BLM RecQ-like-helicase (BLM), BRCA1 DNA repair associated (BRCA1), and several RAD family proteins (RAD21, RAD51, RAD51B, RAD51C, RAD54B). Additionally, protein-related processes including: ribosome biogenesis, rRNA processing, ribosome assembly, protein folding, translational initiation, protein maturation, ribosome and ribonucleoprotein complex formation, translation pre-initiation complex formation, and cytoplasmic translation were significantly downregulated. We identified notable genes such as: eukaryotic translation initiation factors (EIF1, EIF1AX, EIF3E and EIF3F, EIF3H, EIF3I, EIF3L and EIF3M), biogenesis of ribosomes BRX1 (BRIX1), MCTS1 re-initiation and release factor (MCTS1), and ribosomal protein subunits (L10a, L11, 12, 13, 14, 15, 18a, 19).

Cellular Responses to Stimuli during THEV infection

The transcriptome profile indicates that THEV infection likely induced the ER-associated protein degradation (ERAD) pathway. The ER is the major site for protein synthesis, folding and quality control, and sorting. It is also accommodates proteins and protein complexes necessary for other cellular functions including innate immune signaling and metabolism, and serves as the site for lipid biosynthesis (31). The ERAD pathway, a ubiquitin-proteasome-dependent process, is a protein quality control system primarily

194 activated for degradation of unwanted byproducts of protein biogenesis, such as misfolded and unassem-
195 bled/orphaned proteins (31). In our results, the THEV-infected samples showed significant increase in
196 ERAD pathway effector proteins such as: valosin containing protein (VCP), ubiquitin recognition factor in
197 ER associated degradation 1 (UFD1), ER degradation enhancing alpha-mannosidase like proteins 1 and
198 3 (EDEM1, EDEM3), cullin 1 (CUL1), and ubiquilin 1 (UBQLN1). Our KEGG pathway (**Table 4B**) and GO
199 (**Figure 4B**) results indicate a significant upregulation of ubiquitin mediated proteolysis with other ubiqui-
200 tination pathway proteins such as: ubiquitin conjugating enzymes (UBE2J2, UBE2E3, UBE2Z), ubiquitin
201 protein ligases (UBE3A, UBE3B), NPL4 homolog ubiquitin recognition factor (NPLOC4), and ubiquitin like
202 modifier activating enzyme 6 (UBA6) showing significant upregulation. Additionally, the heat shock family
203 of chaperone proteins such as: DnaJ heat shock protein family (Hsp40) members (DNAJB11, DNAJB12,
204 DNAJB2, DNAJC10), heat shock protein family A (Hsp70) members (HSPA4L, HSPA5, HSPA8), and heat
205 shock protein 90 alpha family class A member 1 (HSP90AA1) were upregulated. Moreover, the KEGG path-
206 way analysis (**Table 4A**) shows that a significant upregulation in lysosomal degradation, likely an indication
207 of ER-to-lysosome-associated degradation. Taken together, these results suggest that THEV infection trig-
208 gers significant ER-associated protein degradation, which may contribute to cell death.

209 **Cellular Metabolism Changes During THEV Infection**

210 Many viruses, such as hepatitis C virus, human cytomegalovirus, influenza virus, and rhinovirus, have been
211 documented to manipulate cellular metabolism processes to their advantage (16). A common consequence
212 of infection by many viruses is to induce high glucose metabolism in cells. Adenoviruses have also been
213 shown to upregulate energy metabolic pathways such as glycolysis (32). However, our results show a down-
214 regulation in glycolysis, tricarboxylic acid cycle, oxidative phosphorylation, and ATP synthesis (**Table 2B**).
215 These results indicate that THEV infection may modulate cellular energy metabolism processes differently
216 than other adenoviruses. ~~However, the previously documented metabolic changes were seen in primary~~
217 ~~cells; therefore, studies done with primary host cells would be required to confirm this finding.~~

218 **Validation of DEGs by Reverse Transcriptase Quantitative PCR (RT-qPCR)**

219 To validate the RNA-seq results, 12 DEGs (6 upregulated and 5 downregulated) were selected for RT-
220 qPCR. The DEGs were representative of apoptosis (...), ERAD and ubiquitination (...), and ribosome
221 biosynthetic (...) pathways. As shown in **Figure 5**, the RT-qPCR results corroborate the RNA-seq results,
222 further reinforcing the validity of the RNA-seq transcriptomic profile results.

223 **DISCUSSION**

224 We may not have seen a measurable immune response/pathway enrichment in the infected host cells
225 because the these B-cells may likely require other immune cells such as macrophages and T-cells for ac-
226 tivation/mount an immune response. Also, those cytokine measurement were recorded in cell culture or
227 splenocytes (not just B cells). Additionally, cytokines may not play a dominant role in THEV-induced IMS
228 since TNF-blocking drug (thalidomide) only prevented intestinal disease not immunosuppression, suggest-
229 ing that the mechanism of IMS and intestinal disease are distinct. Secondly, the curated data in the GO,
230 and KEGG databases are most complete for human and other model organisms; hence, there may not be
231 enough information curated for turkeys to highlight the anything that is not very strong immune response.

232 **CONCLUSIONS**

233 **MATERIALS AND METHODS**

234 **Cell culture and THEV Infection**

235 The Turkey B-cell line (MDTC-RP19, ATCC CRL-8135) was grown as a suspension culture in 1:1 complete
236 Leibovitz's L-15/McCoy's 5A medium with 10% fetal bovine serum (FBS), 20% chicken serum (ChS), 5%
237 tryptose phosphate broth (TPB), and 1% antibiotic solution (100 U/mL Penicillin and 100 μ g/mL Strepto-
238 mycin), at 41°C in a humidified atmosphere with 5% CO₂. Infected cells were maintained in 1:1 serum-
239 reduced Leibovitz's L15/McCoy's 5A media (SRLM) with 2.5% FBS, 5% ChS, 1.2% TPB, and 1% antibiotic
240 solution. A commercially available THEV vaccine was purchased from Hygieia Biological Labs (VAS strain).
241 The stock virus was titrated using an in-house qPCR assay with titer expressed as genome copy number
242 (GCN)/mL, similar to Mahshoub *et al* (33). Cells were THEV-infected or mock-infected in triplicates or du-
243 plicates, respectively at a multiplicity of infection (MOI) of 100 GCN/cell, incubated at 41°C for 1 hour, and
244 washed three times with phosphate buffered saline (PBS) to get rid of free virus particles. At each time point
245 (4-, 12-, 24-, and 72-hpi), triplicate (THEV-infected) and duplicate (mock-infected) samples were harvested
246 for total RNA extraction.

247 **RNA extraction and Sequencing**

248 Total RNA was extracted from infected cells using the Thermo Fisher RNAqueous™-4PCR Total RNA Iso-
249 lation Kit (which includes a DNase I digestion step) per manufacturer's instructions. An agarose gel elec-
250 trophoresis was performed to check RNA integrity. The RNA quantity and purity was initially assessed using
251 nanodrop, and RNA was used only if the A260/A280 ratio was 2.0 ± 0.05 and the A260/A230 ratio was >2
252 and <2.2. Extracted total RNA samples were sent to LC Sciences, Houston TX for poly-A-tailed mRNA
253 sequencing. RNA integrity was checked with Agilent Technologies 2100 Bioanalyzer High Sensitivity DNA
254 Chip and poly(A) RNA-seq library was prepared following Illumina's TruSeq-stranded-mRNA sample prepa-
255 ration protocol. Paired-end sequencing, generating 150 bp reads was performed on the Illumina NovaSeq
256 6000 sequencing system. The paired-end 150bp sequences obtained during this study and all expression
257 data have been submitted to the Gene Expression Omnibus database, under accession no #####

258 **Quality Control and Mapping Process**

259 Sequencing reads were processed following a well-established protocol described by Pertea *et al* (19),
260 using Snakemake - version 7.32.4 (34), a popular workflow management system to drive the pipeline.
261 Briefly, raw sequencing reads were trimmed with Cutadapt - version 1.10 (35) and the quality of trimmed
262 reads evaluated using the FastQC software, version 0.12.1 (Bioinformatics Group at the Babraham
263 Institute, Cambridge, United Kingdom; www.bioinformatics.babraham.ac.uk), achieving an overall Mean
264 Sequence Quality (PHRED Score) of 36. Trimmed reads were mapped the reference *Meleagris gallopavo*

265 genome (https://ftp.ncbi.nlm.nih.gov/genomes/all/GCF/000/146/605/GCF_000146605.3_Turkey_5.1/GCF_
266 000146605.3_Turkey_5.1_genomic.fna.gz) with Hisat2 - version 2.2.1 (19) using the accompanying
267 gene transfer format (GTF) annotation file (<https://ftp.ncbi.nlm.nih.gov/genomes/all/GCF/000/146/605/>
268 GCF_000146605.3_Turkey_5.1/GCF_000146605.3_Turkey_5.1_genomic.gtf.gz) to build a genomic index.
269 Samtools - version 1.19.2 was used to convert the output Sequence Alignment Map (SAM) file to the more
270 manageable Binary Alignment Map (BAM) format. The StringTie (v2.2.1) software (19), set to expression
271 estimation mode was used to generate normalized gene expression estimates from the BAM files for genes
272 in the reference GTF file after which the prepDE.py3 script was used to extract read count information from
273 the StringTie gene expression files, providing an expression-count matrix for downstream DEG analysis.

274 **DEG Analysis and Functional Enrichment Analysis**

275 DEG analysis between mock- and THEV-infected samples was performed using the very popular DE-
276 Seq2 (20), which employs a Negative Binomial distribution model for read count comparisons. Genes
277 with $P_{\text{adjusted-value}} \leq 0.05$ were considered as differentially expressed. The read count data are deposited
278 at Gene Expression Omnibus (GEO) under accession number ###. The functional profiling of DEGs (GO
279 and KEGG analyses) were performed based on GO databases and KEGG databases using the R package
280 gprofiler2 (22) with *Meleagris gallopavo* as the reference organism. Results with $P_{\text{adjusted-value}} \leq 0.05$ were
281 included as functionally enriched. Additionally, the DAVID (Database for Annotation, Visualization and Inte-
282 grated Discovery; version 2021) online analysis tool was used for KEGG pathway analysis. All visualization
283 plots were made using ggplot2, pheatmap, and ggvenn R packages (36–38).

284 **Validation of DEGs by Reverse Transcriptase Quantitative PCR (RT-qPCR)**

285 **Statistical Analysis**

286 **DATA AVAILABILITY**

²⁸⁷ **CODE AVAILABILITY**

288 **ACKNOWLEDGMENTS**

289 **REFERENCES**

- 290 1. Harrach B. 2008. Adenoviruses: General features, p. 1–9. In Mahy, BWJ, Van Regenmortel, MHV
(eds.), Encyclopedia of virology (third edition). Book Section. Academic Press, Oxford.
- 291 2. Davison A, Benko M, Harrach B. 2003. Genetic content and evolution of adenoviruses. The Journal
of general virology 84:2895–908.
- 292 3. Gross WB, Moore WE. 1967. Hemorrhagic enteritis of turkeys. Avian Dis 11:296–307.
- 293 4. Beach NM. 2006. Characterization of avirulent turkey hemorrhagic enteritis virus: A study of the
molecular basis for variation in virulence and the occurrence of persistent infection. Thesis.
- 294 5. Dhamma K, Gowthaman V, Karthik K, Tiwari R, Sachan S, Kumar MA, Palanivelu M, Malik YS, Singh
RK, Munir M. 2017. Haemorrhagic enteritis of turkeys – current knowledge. Veterinary Quarterly
37:31–42.
- 295 6. Tykałowski B, Śmiałek M, Koncicki A, Ognik K, Zduńczyk Z, Jankowski J. 2019. The immune re-
sponse of young turkeys to haemorrhagic enteritis virus infection at different levels and sources of
methionine in the diet. BMC Veterinary Research 15.
- 296 7. Pierson F, Fitzgerald S. 2008. Hemorrhagic enteritis and related infections. Diseases of Poultry
276–286.
- 297 8. Rautenschlein S, Sharma JM. 2000. Immunopathogenesis of haemorrhagic enteritis virus (HEV) in
turkeys. Dev Comp Immunol 24:237–46.
- 298 9. Larsen CT, Domermuth CH, Sponenberg DP, Gross WB. 1985. Colibacillosis of turkeys exacerbated
by hemorrhagic enteritis virus. Laboratory studies. Avian Dis 29:729–32.

- 299 10. Beach NM, Duncan RB, Larsen CT, Meng XJ, Sriranganathan N, Pierson FW. 2009. Persistent
infection of turkeys with an avirulent strain of turkey hemorrhagic enteritis virus. *Avian Diseases*
53:370–375.
- 300 11. Rautenschlein S, Suresh M, Sharma JM. 2000. Pathogenic avian adenovirus type II induces apop-
tosis in turkey spleen cells. *Archives of Virology* 145:1671–1683.
- 301 12. Satam H, Joshi K, Mangrolia U, Waghoo S, Zaidi G, Rawool S, Thakare RP, Banday S, Mishra AK,
Das G, Malonia SK. 2023. Next-generation sequencing technology: Current trends and advance-
ments. *Biology* 12:997.
- 302 13. Pandey D, Onkara Perumal P. 2023. A scoping review on deep learning for next-generation RNA-seq.
Data analysis. *Functional & Integrative Genomics* 23.
- 303 14. Wang B, Kumar V, Olson A, Ware D. 2019. Reviving the transcriptome studies: An insight into the
emergence of single-molecule transcriptome sequencing. *Frontiers in Genetics* 10.
- 304 15. Choi SC. 2016. On the study of microbial transcriptomes using second- and third-generation se-
quencing technologies. *Journal of Microbiology* 54:527–536.
- 305 16. Mo Q, Feng K, Dai S, Wu Q, Zhang Z, Ali A, Deng F, Wang H, Ning Y-J. 2023. Transcriptome
profiling highlights regulated biological processes and type III interferon antiviral responses upon
crimean-congo hemorrhagic fever virus infection. *Virologica Sinica* 38:34–46.
- 306 17. Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, Davis AP, Dolinski K, Dwight
SS, Eppig JT, Harris MA, Hill DP, Issel-Tarver L, Kasarskis A, Lewis S, Matese JC, Richardson JE,
Ringwald M, Rubin GM, Sherlock G. 2000. Gene ontology: Tool for the unification of biology. *Nature
Genetics* 25:25–29.
- 307 18. Kanehisa M. 2000. KEGG: Kyoto encyclopedia of genes and genomes. *Nucleic Acids Research*
28:27–30.

- 308 19. Pertea M, Kim D, Pertea GM, Leek JT, Salzberg SL. 2016. Transcript-level expression analysis of
RNA-seq experiments with HISAT, StringTie and ballgown. *Nature Protocols* 11:1650–1667.
- 309 20. Love MI, Huber W, Anders S. 2014. Moderated estimation of fold change and dispersion for RNA-seq
data with DESeq2. *Genome Biology* 15:550.
- 310 21. Sherman BT, Hao M, Qiu J, Jiao X, Baseler MW, Lane HC, Imamichi T, Chang W. 2022. DAVID: A
web server for functional enrichment analysis and functional annotation of gene lists (2021 update).
Nucleic Acids Research 50:W216–W221.
- 311 22. Kolberg L, Raudvere U, Kuzmin I, Vilo J, Peterson H. 2020. gprofiler2— an r package for gene
list functional enrichment analysis and namespace conversion toolset g:profiler. *F1000Research* 9
(ELIXIR).
- 312 23. Saunders GK, Pierson FW, Hurk JV van den. 1993. Haemorrhagic enteritis virus infection in turkeys:
A comparison of virulent and avirulent virus infections, and a proposed pathogenesis. *Avian Pathology* 22:47–58.
- 313 24. Barber GN. 2001. Host defense, viruses and apoptosis. *Cell Death & Differentiation* 8:113–126.
- 314 25. Hardwick JM. 1997. Virus-induced apoptosis, p. 295–336. *In Apoptosis - pharmacological implications and therapeutic opportunities*. Elsevier.
- 315 26. Verburg SG, Lelievre RM, Westerveld MJ, Inkol JM, Sun YL, Workenhe ST. 2022. Viral-mediated
activation and inhibition of programmed cell death. *PLOS Pathogens* 18:e1010718.
- 316 27. Ezoe H, Fatt RB, Mak S. 1981. Degradation of intracellular DNA in KB cells infected with cyt mutants
of human adenovirus type 12. *Journal of Virology* 40:20–27.
- 317 28. Quaye A, Pickett BE, Griffitts JS, Berges BK, Poole BD. 2024. Characterizing the splice map of
turkey hemorrhagic enteritis virus. *Virology Journal* 21.

- 318 29. Roos WP, Kaina B. 2006. DNA damage-induced cell death by apoptosis. *Trends in Molecular Medicine* 12:440–450.
- 319 30. Martin SJ. 1993. Protein or RNA synthesis inhibition induces apoptosis of mature human CD4+ t cell blasts. *Immunology Letters* 35:125–134.
- 320 31. Christianson JC, Carvalho P. 2022. Order through destruction: How ER-associated protein degradation contributes to organelle homeostasis. *The EMBO Journal* 41.
- 321 32. Thai M, Graham NA, Braas D, Nehil M, Komisopoulou E, Kurdistani SK, McCormick F, Graeber TG, Christofk HR. 2014. Adenovirus E4ORF1-induced MYC activation promotes host cell anabolic glucose metabolism and virus replication. *Cell Metabolism* 19:694–701.
- 322 33. Mahsoub HM, Evans NP, Beach NM, Yuan L, Zimmerman K, Pierson FW. 2017. Real-time PCR-based infectivity assay for the titration of turkey hemorrhagic enteritis virus, an adenovirus, in live vaccines. *Journal of Virological Methods* 239:42–49.
- 323 34. Mölder F, Jablonski KP, Letcher B, Hall MB, Tomkins-Tinch CH, Sochat V, Forster J, Lee S, Twardziok SO, Kanitz A, Wilm A, Holtgrewe M, Rahmann S, Nahnsen S, Köster J. 2021. Sustainable data analysis with snakemake. *F1000Research* 10:33.
- 324 35. Martin M. 2011. Cutadapt removes adapter sequences from high-throughput sequencing reads. *EMBnetjournal* 17:10.
- 325 36. Wickham H. 2016. *ggplot2: Elegant graphics for data analysis*. Springer-Verlag New York. <https://ggplot2.tidyverse.org>.
- 326 37. Kolde R. 2019. *Pheatmap: Pretty heatmaps*. <https://CRAN.R-project.org/package=pheatmap>.
- 327 38. Yan L. 2023. *Ggvenn: Draw venn diagram by 'ggplot2'*. <https://CRAN.R-project.org/package=ggvenn>.

328 TABLES AND FIGURES

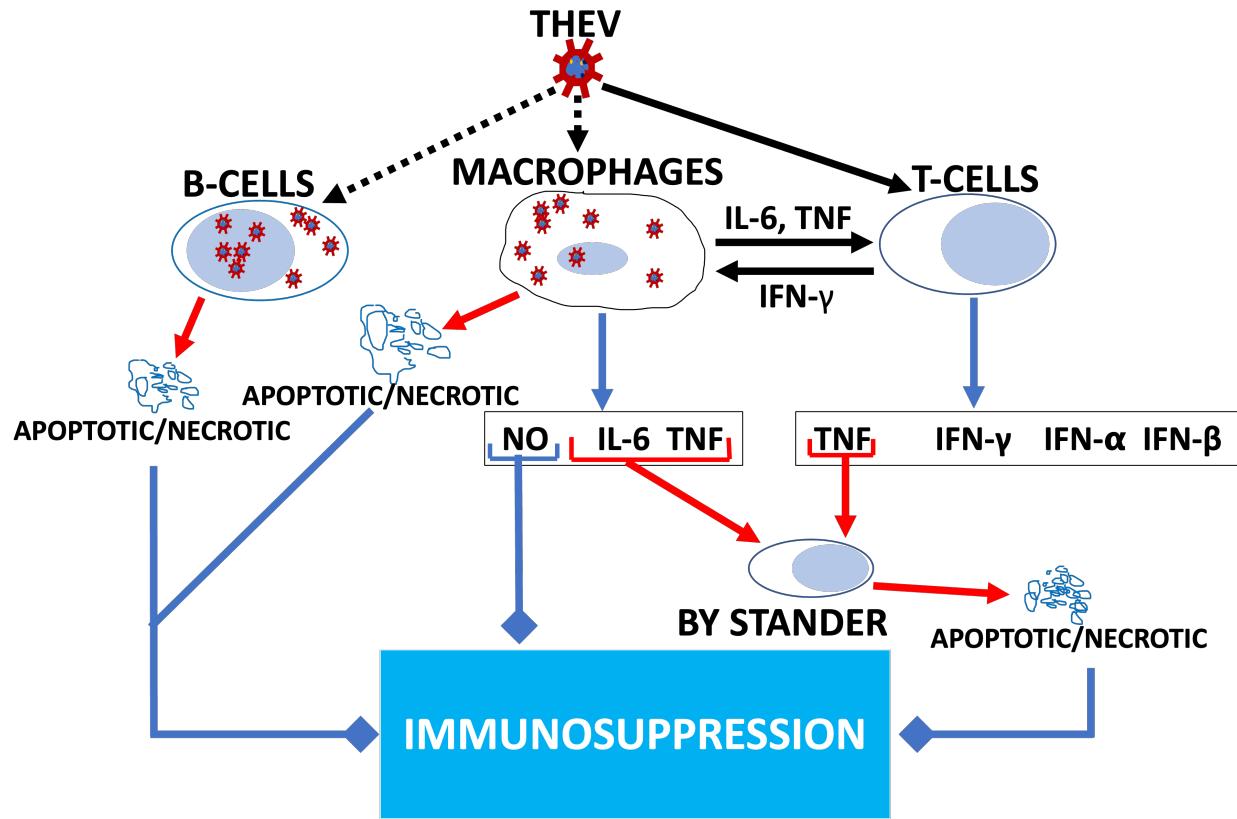


Figure 1: Model of THEV-induced immunosuppression in turkeys. THEV infection of target cells is indicated with black dotted arrows. Black unbroken arrows indicate cell activation. Red arrows indicate signals leading to apoptosis. Blue arrows indicate all cytokines released by the cell. Blue arrows with square heads indicate an event leading to IMS. Adapted from Rautenschlein *et al.* (8).

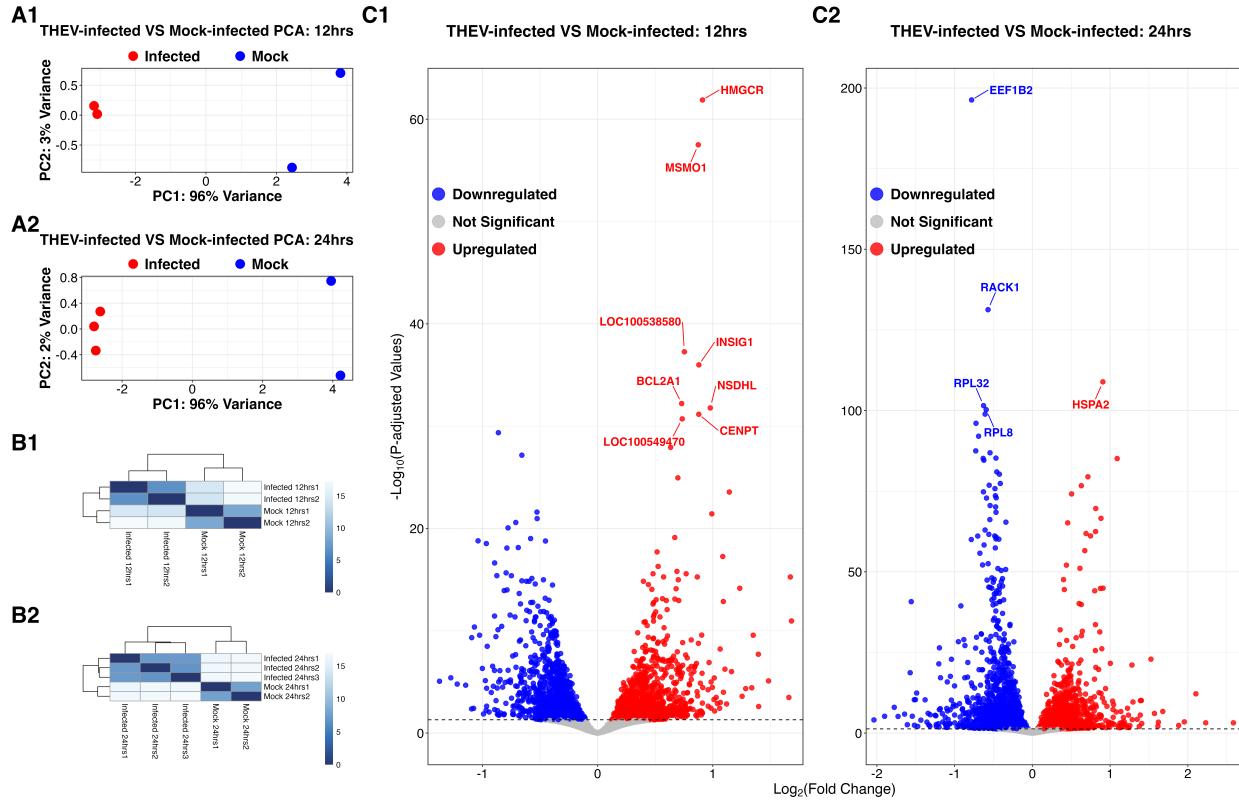


Figure 2. (A) Principal component analysis (PCA) of turkey B-cells during THEV infection. At 12-hpi (**A1**), the results indicate that the first (PC1) and second (PC2) principal components account for 96% and 3% of the variation in the samples, respectively. Whereas PC1 and PC2 account for 96% and 2% of the variation, respectively at 24-hpi (**A2**). **(B) Poisson distance matrices illustrating the RNA-seq library integrity within treatment (infected versus mock) groups.** The color scale represents the distances between biological replicates for both 12-hpi samples (**B1**) and 24-hpi samples (**B2**). Dark colors represent high correlation (similarity) between the samples involved. **(C) Volcano plots of DEGs between THEV-infected versus mock-infected cells at 12- and 24-hpi.** Red, blue, and grey dots represent upregulated, downregulated, and non-significant genes, respectively for both 12-hpi samples (**C1**) and 24-hpi samples (**C2**).

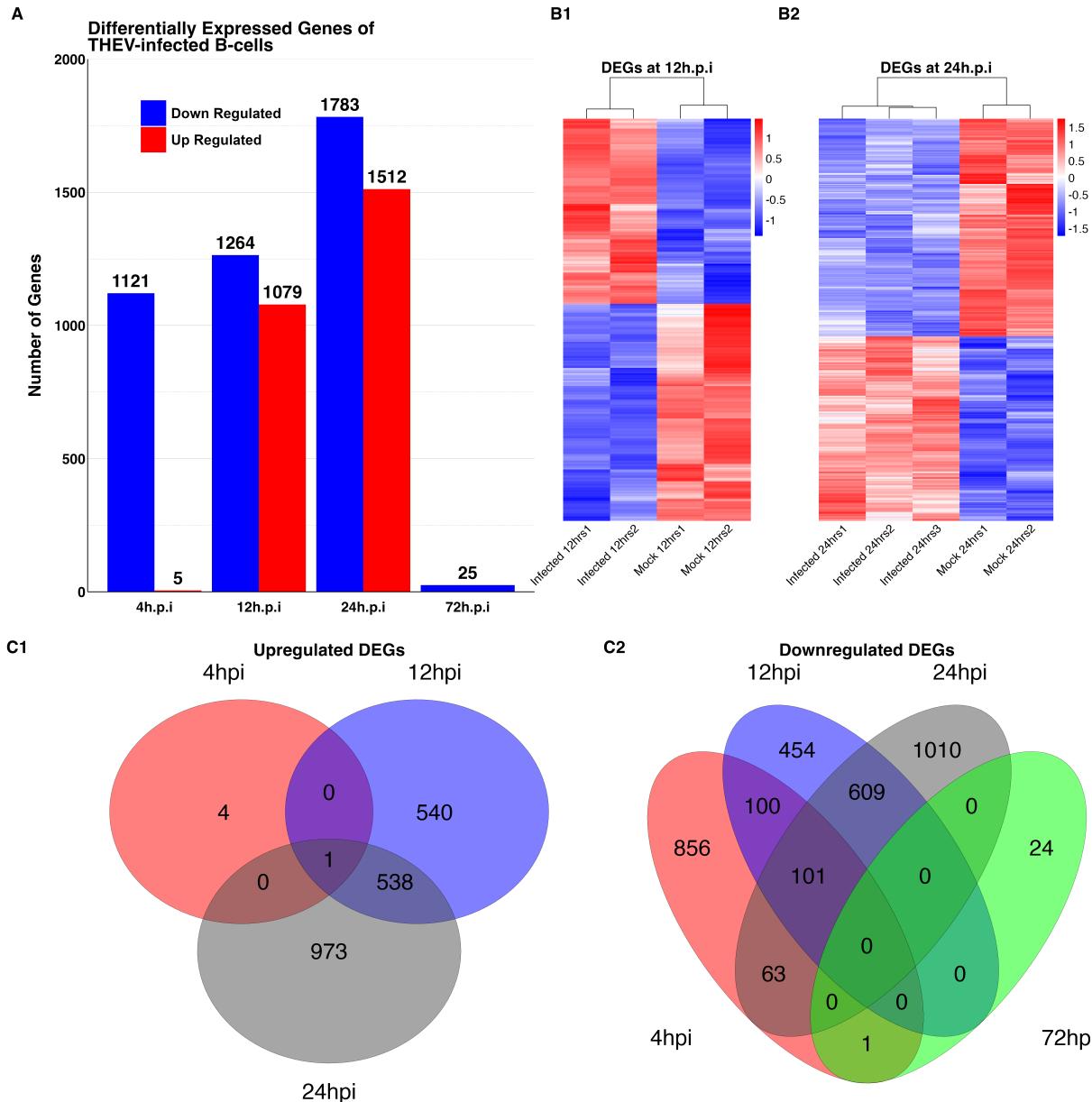


Figure 3: DEGs of THEV-infected versus mock-infected samples at different time points. (A) Bar plot of number DEGs identified. Red represents upregulated genes and blue represents downregulated genes. **(B) Heatmaps of scaled expression data (Z-scores) of DEGs.** DEGs identified at 12-hpi are shown in (B1) and DEGs at 24-hpi in (B2). **(C) Venn diagrams showing the number of DEGs identified at different time points.** For the upregulated genes (C1), the red circle represents genes at 4-hpi, the blue circle, 12-hpi, and the grey circle, 24-hpi. For the downregulated genes (C2), the green circle represents genes at 72-hpi, while all the other time points retain the colors from (C1).

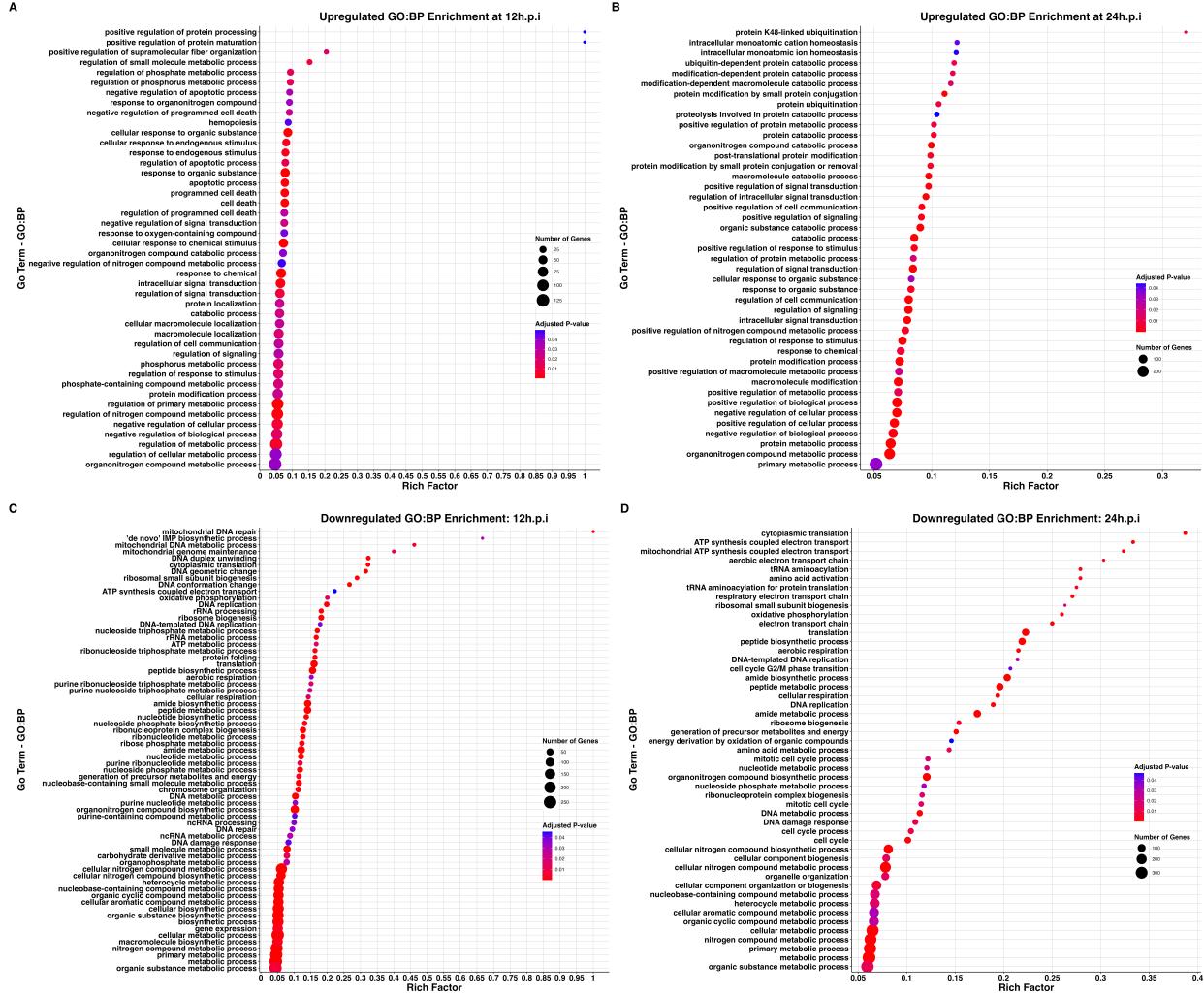


Figure 4: Dotplot of Enriched Gene Ontology Biological Processes (BP). Significant BP GO terms identified for upregulated DEGs at 12-hpi and 24-hpi are shown in (A) and (B), respectively. Significant BP GO terms for downregulated DEGs at 12-hpi and 24-hpi are shown in (C) and (D), respectively. The y-axis indicates GO terms and the x-axis represents the rich factor, which indicates the ratio of the number of DEGs annotated to the term to the total number of genes annotated to the term. The diameter indicates the number of genes overlapping the gene ontology term and the color indicates the enrichment P-value.

Table 1: Summary of sequencing, quality control, and mapping processes

Sample	Raw Reads ^M	Trimmed Reads ^M	Mapped Reads ^M	Uniquely Mapped	Non-uniquely	Q20%	Q30%	GC
				Reads ^M	Mapped Reads ^M			Content (%)
I_12hrsS1 ^{Inf}	40.6	39.0	34.7 (88.92%)	33.1 (84.78%)	1.6 (4.14%)	99.95	97.23	47.5
I_12hrsS3 ^{Inf}	38.8	37.3	33.1 (88.78%)	31.7 (84.95%)	1.4 (3.83%)	99.95	97.53	47.5
I_24hrsS1 ^{Inf}	42.7	41.0	36.2 (88.13%)	34.5 (84.2%)	1.6 (3.93%)	99.95	96.95	46.5
I_24hrsS2 ^{Inf}	42.0	40.4	35.6 (88.1%)	33.9 (83.83%)	1.7 (4.27%)	99.94	97.05	46.5
I_24hrsS3 ^{Inf}	40.5	38.9	34.2 (88.01%)	32.7 (84.12%)	1.5 (3.89%)	99.95	97.08	47.0
I_4hrsS1 ^{Inf}	39.1	37.4	33 (88.16%)	31.2 (83.43%)	1.8 (4.73%)	99.93	97.04	48.5
I_4hrsS2 ^{Inf}	41.3	39.6	35.3 (89.24%)	33.6 (84.92%)	1.7 (4.33%)	99.95	97.15	47.0
I_4hrsS3 ^{Inf}	41.5	39.8	35.5 (89.2%)	33.2 (83.29%)	2.4 (5.91%)	99.95	97.11	47.5
I_72hrsS1 ^{Inf}	41.2	39.8	28.3 (71.09%)	26.9 (67.7%)	1.3 (3.38%)	99.96	97.23	44.5
I_72hrsS2 ^{Inf}	39.3	38.0	27 (71.11%)	25.8 (67.86%)	1.2 (3.25%)	99.96	97.34	44.5
I_72hrsS3 ^{Inf}	39.9	37.1	28.3 (76.36%)	26.1 (70.3%)	2.2 (6.05%)	99.87	96.14	52.5
U_12hrsN1 ^{Mk}	42.1	40.4	35.9 (88.72%)	34.1 (84.39%)	1.7 (4.33%)	99.95	97.04	47.5
U_12hrsN2 ^{Mk}	41.0	39.3	34.7 (88.4%)	33.2 (84.53%)	1.5 (3.86%)	99.94	97.08	47.5
U_24hrsN1 ^{Mk}	38.4	37.0	32.7 (88.46%)	31.4 (84.74%)	1.4 (3.72%)	99.96	97.48	47.5
U_24hrsN2 ^{Mk}	39.9	38.4	34 (88.58%)	32.6 (84.96%)	1.4 (3.61%)	99.95	96.95	47.0
U_4hrsN1 ^{Mk}	39.4	37.9	33.7 (88.9%)	32 (84.41%)	1.7 (4.49%)	99.96	97.36	47.0
U_4hrsN2 ^{Mk}	37.6	34.7	22 (63.43%)	18.5 (53.18%)	3.6 (10.25%)	99.80	94.96	61.0
U_72hrsN1 ^{Mk}	50.3	47.9	15.5 (32.4%)	11.7 (24.5%)	3.8 (7.9%)	99.88	96.54	56.0
U_72hrsN2 ^{Mk}	40.5	38.9	34.5 (88.82%)	32.7 (84.14%)	1.8 (4.68%)	99.95	97.04	46.5

Sample	Raw Reads ^M	Trimmed Reads ^M	Mapped Reads ^M	Uniquely Mapped Reads ^M	Non-uniquely Mapped Reads ^M	Q20%	Q30%	GC Content (%)
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^MAll values for number of reads are in millions;

^{Inf}These are infected samples indicated by the letter 'I' and 'S' in sample names

^{Mk}These are mock-infected samples indicated by the letters 'U' and 'N' in sample names

Table 2A: Gene ontology analysis of Significantly Upregulated DEGs identified at 12-hpi

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
Biological Process				
GO:BP	regulation of metabolic process	1.47	279	6.08e-09
GO:BP	regulation of cellular metabolic process	1.48	252	2.56e-08
GO:BP	programmed cell death	2.85	51	4.99e-08
GO:BP	cell death	2.85	51	4.99e-08
GO:BP	negative regulation of cellular process	1.59	174	1.90e-07
GO:BP	negative regulation of biological process	1.56	187	1.90e-07
GO:BP	apoptotic process	2.75	47	6.09e-07
GO:BP	regulation of macromolecule metabolic process	1.42	248	9.05e-07
GO:BP	protein phosphorylation	2.33	61	9.07e-07
GO:BP	phosphate-containing compound metabolic process	1.63	145	1.11e-06
GO:BP	phosphorus metabolic process	1.63	146	1.11e-06
GO:BP	regulation of primary metabolic process	1.40	226	1.02e-05

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	secondary alcohol biosynthetic process	7.67	13	1.58e-05
GO:BP	regulation of cellular biosynthetic process	1.41	210	2.24e-05
GO:BP	sterol biosynthetic process	7.24	13	2.79e-05
GO:BP	regulation of apoptotic process	2.15	57	2.79e-05
GO:BP	protein modification process	1.55	138	3.56e-05
GO:BP	regulation of biosynthetic process	1.40	210	3.56e-05
GO:BP	macromolecule localization	1.58	128	3.56e-05
GO:BP	small molecule biosynthetic process	2.38	45	3.75e-05
GO:BP	phytosteroid biosynthetic process	12.04	9	3.75e-05
GO:BP	phytosteroid metabolic process	12.04	9	3.75e-05
GO:BP	regulation of macromolecule biosynthetic process	1.39	205	6.25e-05
GO:BP	regulation of programmed cell death	2.07	57	6.77e-05
GO:BP	negative regulation of cellular metabolic process	1.79	80	9.46e-05
GO:BP	regulation of gene expression	1.38	201	1.06e-04
GO:BP	primary metabolic process	1.22	380	1.08e-04
GO:BP	negative regulation of metabolic process	1.70	91	1.10e-04
GO:BP	cellular response to stress	1.77	81	1.11e-04
GO:BP	phosphorylation	1.80	74	1.96e-04
GO:BP	alcohol biosynthetic process	3.77	19	3.45e-04
GO:BP	metabolic process	1.19	426	3.93e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	organonitrogen compound metabolic process	1.29	260	3.93e-04
GO:BP	protein localization	1.58	104	4.21e-04
GO:BP	regulation of cellular process	1.16	473	4.21e-04
GO:BP	cellular macromolecule localization	1.58	104	4.21e-04
GO:BP	negative regulation of programmed cell death	2.35	37	4.29e-04
GO:BP	cellular localization	1.45	145	4.34e-04
GO:BP	positive regulation of metabolic process	1.53	116	4.34e-04
GO:BP	negative regulation of apoptotic process	2.37	36	4.54e-04
GO:BP	regulation of biological process	1.15	497	5.83e-04
GO:BP	intracellular protein transport	2.00	50	5.94e-04
GO:BP	establishment of localization in cell	1.56	104	5.94e-04
GO:BP	ergosterol biosynthetic process	12.77	7	5.94e-04
GO:BP	ergosterol metabolic process	12.77	7	5.94e-04
GO:BP	negative regulation of macromolecule metabolic process	1.66	82	7.20e-04
GO:BP	cholesterol biosynthetic process	6.92	10	7.48e-04
GO:BP	apoptotic signaling pathway	3.32	20	8.19e-04
GO:BP	biological regulation	1.14	517	8.20e-04
GO:BP	mitotic cell cycle process	2.14	41	8.20e-04
GO:BP	regulation of catabolic process	2.01	47	8.20e-04
GO:BP	steroid biosynthetic process	3.96	16	8.52e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	negative regulation of gene expression	2.16	40	8.52e-04
GO:BP	cellular metabolic process	1.23	307	8.52e-04
GO:BP	positive regulation of cellular metabolic process	1.56	98	8.52e-04
GO:BP	negative regulation of cellular biosynthetic process	1.74	68	8.52e-04
GO:BP	macromolecule modification	1.43	138	9.09e-04
GO:BP	positive regulation of apoptotic process	2.85	24	9.34e-04
GO:BP	negative regulation of biosynthetic process	1.73	68	1.03e-03
GO:BP	catabolic process	1.51	108	1.03e-03
GO:BP	protein localization to organelle	1.90	52	1.15e-03
GO:BP	response to chemical	1.56	95	1.24e-03
GO:BP	positive regulation of biological process	1.33	193	1.29e-03
GO:BP	regulation of nucleobase-containing compound metabolic process	1.36	167	1.29e-03
GO:BP	cell cycle	1.68	72	1.34e-03
GO:BP	intracellular signal transduction	1.54	97	1.48e-03
GO:BP	positive regulation of programmed cell death	2.74	24	1.58e-03
GO:BP	mitotic cell cycle	1.94	47	1.70e-03
GO:BP	macromolecule catabolic process	1.76	60	1.77e-03
GO:BP	positive regulation of cellular process	1.34	173	1.83e-03
GO:BP	sterol metabolic process	3.86	15	1.83e-03
GO:BP	lipid biosynthetic process	1.94	46	1.94e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	negative regulation of macromolecule biosynthetic process	1.70	65	2.25e-03
GO:BP	regulation of response to stress	1.91	46	2.54e-03
GO:BP	cellular lipid metabolic process	1.67	67	3.03e-03
GO:BP	organic hydroxy compound biosynthetic process	2.93	20	3.11e-03
GO:BP	cellular lipid biosynthetic process	9.36	7	3.16e-03
GO:BP	regulation of response to stimulus	1.39	137	3.49e-03
GO:BP	establishment of protein localization	1.61	73	3.79e-03
GO:BP	response to stress	1.44	112	3.79e-03
GO:BP	nitrogen compound transport	1.57	79	4.15e-03
GO:BP	response to oxygen-containing compound	1.90	44	4.16e-03
GO:BP	process utilizing autophagic mechanism	2.59	23	4.43e-03
GO:BP	autophagy	2.59	23	4.43e-03
GO:BP	regulation of intracellular signal transduction	1.60	73	4.75e-03
GO:BP	secondary alcohol metabolic process	3.70	14	4.85e-03
GO:BP	regulation of signal transduction	1.44	110	4.85e-03
GO:BP	cell cycle process	1.70	59	4.85e-03
GO:BP	regulation of developmental process	1.59	73	4.88e-03
GO:BP	macroautophagy	2.98	18	5.47e-03
GO:BP	response to lipid	2.41	25	5.91e-03
GO:BP	positive regulation of macromolecule metabolic process	1.46	100	5.97e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	regulation of RNA metabolic process	1.34	154	5.97e-03
GO:BP	macromolecule metabolic process	1.21	286	6.45e-03
GO:BP	positive regulation of catabolic process	2.30	27	6.45e-03
GO:BP	regulation of DNA-templated transcription	1.35	142	7.41e-03
GO:BP	establishment of protein localization to organelle	2.04	34	7.41e-03
GO:BP	lipid metabolic process	1.53	79	7.41e-03
GO:BP	response to organonitrogen compound	2.19	29	7.59e-03
GO:BP	regulation of RNA biosynthetic process	1.35	142	7.59e-03
GO:BP	endoderm development	6.42	8	7.66e-03
GO:BP	mRNA transcription	7.80	7	7.79e-03
GO:BP	regulation of transcription by RNA polymerase II	1.41	111	7.98e-03
GO:BP	cellular response to lipid	2.66	20	8.44e-03
GO:BP	protein metabolic process	1.27	198	8.44e-03
GO:BP	nuclear-transcribed mRNA catabolic process, deadenylation-independent decay	14.33	5	8.47e-03
GO:BP	deadenylation-independent decapping of nuclear-transcribed mRNA	14.33	5	8.47e-03
GO:BP	gland development	3.06	16	9.41e-03
GO:BP	vesicle-mediated transport	1.51	80	9.41e-03
GO:BP	multicellular organismal-level homeostasis	2.48	22	9.41e-03
GO:BP	embryonic morphogenesis	2.36	24	9.41e-03
GO:BP	regulation of autophagy	2.61	20	1.02e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	intracellular transport	1.51	79	1.02e-02
GO:BP	organophosphate metabolic process	1.59	65	1.09e-02
GO:BP	cholesterol metabolic process	3.76	12	1.20e-02
GO:BP	small molecule metabolic process	1.44	93	1.24e-02
GO:BP	regulation of signaling	1.37	121	1.25e-02
GO:BP	localization	1.24	219	1.25e-02
GO:BP	homeostasis of number of cells	3.27	14	1.27e-02
GO:BP	cellular response to oxygen levels	5.02	9	1.27e-02
GO:BP	intrinsic apoptotic signaling pathway	3.70	12	1.31e-02
GO:BP	cell division	2.20	26	1.31e-02
GO:BP	regulation of cell communication	1.36	120	1.31e-02
GO:BP	cellular component disassembly	2.46	21	1.31e-02
GO:BP	protein transport	1.58	62	1.45e-02
GO:BP	establishment or maintenance of cell polarity	2.51	20	1.48e-02
GO:BP	DNA-templated transcription	2.17	26	1.53e-02
GO:BP	developmental growth	2.58	19	1.53e-02
GO:BP	growth	2.58	19	1.53e-02
GO:BP	hemopoiesis	2.16	26	1.69e-02
GO:BP	biological process involved in interspecies interaction between organisms	1.80	40	1.74e-02
GO:BP	negative regulation of intracellular signal transduction	2.07	28	1.78e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	extrinsic apoptotic signaling pathway	4.18	10	1.89e-02
GO:BP	cellular response to oxygen-containing compound	1.92	33	1.98e-02
GO:BP	regulation of cellular catabolic process	2.35	21	2.18e-02
GO:BP	response to nitrogen compound	1.97	30	2.46e-02
GO:BP	steroid metabolic process	2.54	18	2.46e-02
GO:BP	establishment of localization	1.24	195	2.46e-02
GO:BP	cellular response to chemical stimulus	1.56	60	2.49e-02
GO:BP	regulation of cytokine production	2.21	23	2.61e-02
GO:BP	regulation of epithelial cell apoptotic process	5.02	8	2.79e-02
GO:BP	intracellular lipid transport	5.02	8	2.79e-02
GO:BP	cellular response to hypoxia	5.02	8	2.79e-02
GO:BP	nuclear transport	2.24	22	2.79e-02
GO:BP	nucleocytoplasmic transport	2.24	22	2.79e-02
GO:BP	positive regulation of signal transduction	1.62	51	2.85e-02
GO:BP	regulation of phosphate metabolic process	1.79	37	2.89e-02
GO:BP	regulation of phosphorus metabolic process	1.79	37	2.89e-02
GO:BP	cellular response to lipopolysaccharide	3.56	11	2.92e-02
GO:BP	androgen receptor signaling pathway	10.03	5	3.18e-02
GO:BP	motor neuron apoptotic process	10.03	5	3.18e-02
GO:BP	cellular response to decreased oxygen levels	4.86	8	3.18e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	transport	1.24	183	3.18e-02
GO:BP	purine nucleoside bisphosphate metabolic process	3.03	13	3.39e-02
GO:BP	ribonucleoside bisphosphate metabolic process	3.03	13	3.39e-02
GO:BP	nucleoside bisphosphate metabolic process	3.03	13	3.39e-02
GO:BP	appendage development	4.20	9	3.40e-02
GO:BP	limb development	4.20	9	3.40e-02
GO:BP	embryo development	1.93	29	3.43e-02
GO:BP	cellular response to biotic stimulus	3.21	12	3.47e-02
GO:BP	regulation of leukocyte differentiation	3.00	13	3.64e-02
GO:BP	regulation of cell cycle	1.67	43	3.66e-02
GO:BP	tissue development	1.58	51	4.22e-02
GO:BP	limb morphogenesis	4.59	8	4.22e-02
GO:BP	appendage morphogenesis	4.59	8	4.22e-02
GO:BP	mitotic cell cycle phase transition	3.34	11	4.22e-02
GO:BP	cellular response to molecule of bacterial origin	3.34	11	4.22e-02
GO:BP	positive regulation of cell communication	1.55	55	4.22e-02
GO:BP	positive regulation of signaling	1.55	55	4.22e-02
GO:BP	cellular catabolic process	1.64	44	4.22e-02
GO:BP	nucleobase-containing compound catabolic process	2.05	24	4.40e-02
GO:BP	protein catabolic process	1.66	42	4.40e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	cell cycle phase transition	3.29	11	4.63e-02
GO:BP	regulation of cell cycle process	1.79	33	4.65e-02
GO:BP	regulation of anatomical structure morphogenesis	1.81	32	4.74e-02
GO:BP	regulation of mitotic cell cycle phase transition	2.34	18	4.74e-02
GO:BP	positive regulation of cellular biosynthetic process	1.44	72	4.95e-02
GO:BP	regulation of protein metabolic process	1.50	59	4.97e-02
Cellular Component				
GO:CC	intracellular anatomical structure	1.19	774	8.23e-20
GO:CC	cytoplasm	1.28	590	7.06e-17
GO:CC	intracellular membrane-bounded organelle	1.29	578	1.08e-16
GO:CC	membrane-bounded organelle	1.26	595	7.52e-16
GO:CC	intracellular organelle	1.23	655	7.52e-16
GO:CC	organelle	1.21	666	2.49e-14
GO:CC	nucleus	1.42	371	1.33e-13
GO:CC	cytosol	1.69	166	6.96e-10
GO:CC	organelle membrane	1.59	154	3.53e-07
GO:CC	endomembrane system	1.48	200	3.53e-07
GO:CC	nucleoplasm	1.75	104	1.57e-06
GO:CC	bounding membrane of organelle	1.70	92	3.49e-05
GO:CC	intracellular organelle lumen	1.51	135	4.91e-05

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	organelle lumen	1.51	135	4.91e-05
GO:CC	membrane-enclosed lumen	1.51	135	4.91e-05
GO:CC	nuclear lumen	1.55	119	6.06e-05
GO:CC	cytoplasmic vesicle	1.57	88	1.12e-03
GO:CC	intracellular vesicle	1.55	88	1.62e-03
GO:CC	vesicle	1.51	95	1.94e-03
GO:CC	endoplasmic reticulum	1.54	86	2.07e-03
GO:CC	perinuclear region of cytoplasm	2.51	25	2.11e-03
GO:CC	chromatin	1.84	40	9.58e-03
GO:CC	chromosome	1.58	63	1.10e-02
GO:CC	organelle subcompartment	1.56	65	1.21e-02
GO:CC	endosome	1.69	48	1.37e-02
GO:CC	Golgi apparatus	1.52	69	1.40e-02
GO:CC	protein-DNA complex	1.76	42	1.40e-02
GO:CC	vesicle membrane	1.74	43	1.40e-02
GO:CC	transcription regulator complex	1.99	30	1.40e-02
GO:CC	vacuole	1.82	34	2.73e-02
GO:CC	phagophore assembly site	4.73	8	2.83e-02
GO:CC	spindle	2.04	25	2.85e-02
GO:CC	cytoplasmic vesicle membrane	1.69	41	2.85e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	endosome membrane	2.02	25	3.21e-02
GO:CC	early endosome	2.11	22	3.70e-02
Molecular Function				
GO:MF	enzyme binding	2.20	102	8.60e-11
GO:MF	protein binding	1.27	427	8.52e-08
GO:MF	protein-macromolecule adaptor activity	1.98	67	5.57e-05
GO:MF	molecular adaptor activity	1.90	73	5.57e-05
GO:MF	identical protein binding	2.07	54	1.96e-04
GO:MF	binding	1.09	714	4.02e-04
GO:MF	kinase activity	1.58	86	4.95e-03
GO:MF	transferase activity, transferring phosphorus-containing groups	1.51	96	5.83e-03
GO:MF	kinase binding	2.14	35	5.83e-03
GO:MF	phosphotransferase activity, alcohol group as acceptor	1.59	80	5.83e-03
GO:MF	DNA-binding transcription factor binding	2.73	22	5.83e-03
GO:MF	small molecule binding	1.19	338	5.83e-03
GO:MF	protein domain specific binding	2.51	25	5.83e-03
GO:MF	transcription factor binding	2.38	27	6.59e-03
GO:MF	RNA polymerase II-specific DNA-binding transcription factor binding	2.94	18	1.05e-02
GO:MF	ion binding	1.19	325	1.05e-02
GO:MF	manganese ion binding	5.62	9	1.05e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:MF	transferase activity	1.30	176	1.05e-02
GO:MF	transcription coregulator activity	1.93	38	1.18e-02
GO:MF	protein kinase binding	2.10	31	1.18e-02
GO:MF	protein kinase activity	1.59	67	1.20e-02
GO:MF	enzyme regulator activity	1.50	82	1.38e-02
GO:MF	nuclear androgen receptor binding	12.88	5	1.83e-02
GO:MF	protein homodimerization activity	2.29	23	2.51e-02
GO:MF	ATP binding	1.33	128	2.71e-02
GO:MF	adenyl ribonucleotide binding	1.33	130	2.71e-02
GO:MF	myosin phosphatase activity	4.64	9	2.71e-02
GO:MF	signaling adaptor activity	3.44	12	3.01e-02
GO:MF	R-SMAD binding	10.31	5	4.03e-02
GO:MF	protein serine/threonine kinase activity	1.68	44	4.27e-02
GO:MF	purine ribonucleoside triphosphate binding	1.28	148	4.38e-02
GO:MF	adenyl nucleotide binding	1.30	133	4.38e-02

Table 2B: Gene ontology analysis of Significantly Downregulated DEGs identified at 12-hpi

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
Biological Process				

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	gene expression	3.07	289	4.61e-70
GO:BP	macromolecule biosynthetic process	2.69	313	8.24e-63
GO:BP	biosynthetic process	2.25	377	3.04e-57
GO:BP	translation	6.31	110	7.08e-55
GO:BP	cellular biosynthetic process	2.29	329	4.05e-50
GO:BP	ribonucleoprotein complex biogenesis	5.52	108	1.71e-47
GO:BP	metabolic process	1.57	618	9.00e-47
GO:BP	cellular metabolic process	1.77	482	3.42e-45
GO:BP	macromolecule metabolic process	1.79	466	6.20e-45
GO:BP	nucleobase-containing compound metabolic process	2.41	276	9.74e-45
GO:BP	primary metabolic process	1.63	556	1.30e-44
GO:BP	nucleic acid metabolic process	2.56	226	1.57e-39
GO:BP	ribosome biogenesis	5.80	86	2.32e-39
GO:BP	organonitrogen compound biosynthetic process	2.74	170	3.69e-32
GO:BP	nucleobase-containing compound biosynthetic process	2.57	178	2.25e-30
GO:BP	rRNA processing	5.97	62	1.61e-28
GO:BP	rRNA metabolic process	5.57	63	4.00e-27
GO:BP	RNA processing	3.04	120	6.65e-26
GO:BP	RNA metabolic process	2.49	152	6.25e-24
GO:BP	nucleic acid biosynthetic process	2.57	142	1.38e-23

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	RNA biosynthetic process	2.55	135	4.64e-22
GO:BP	ribosomal large subunit biogenesis	8.18	34	8.01e-20
GO:BP	protein-RNA complex assembly	5.76	40	3.24e-17
GO:BP	cytoplasmic translation	9.15	27	7.21e-17
GO:BP	protein-RNA complex organization	5.54	40	1.35e-16
GO:BP	ribosomal small subunit biogenesis	7.36	31	2.14e-16
GO:BP	DNA replication	4.95	39	2.28e-14
GO:BP	organonitrogen compound metabolic process	1.50	331	2.81e-14
GO:BP	DNA metabolic process	2.74	82	3.18e-14
GO:BP	cellular component biogenesis	1.83	182	5.57e-14
GO:BP	DNA-templated DNA replication	5.29	33	8.34e-13
GO:BP	protein metabolic process	1.52	261	2.39e-11
GO:BP	ribosome assembly	8.13	20	6.51e-11
GO:BP	aerobic respiration	5.10	29	1.17e-10
GO:BP	protein folding	4.00	35	6.76e-10
GO:BP	oxidative phosphorylation	6.29	22	1.17e-09
GO:BP	protein-containing complex organization	1.95	112	1.17e-09
GO:BP	protein-containing complex assembly	2.19	83	2.81e-09
GO:BP	cellular respiration	4.50	29	2.81e-09
GO:BP	DNA damage response	2.35	69	7.26e-09

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	maturation of LSU-rRNA	8.13	16	1.88e-08
GO:BP	ATP synthesis coupled electron transport	6.10	18	1.95e-07
GO:BP	nucleoside triphosphate metabolic process	3.95	27	2.73e-07
GO:BP	cellular process	1.10	827	3.50e-07
GO:BP	maturation of SSU-rRNA	6.22	17	4.15e-07
GO:BP	electron transport chain	5.08	20	5.49e-07
GO:BP	mitochondrial ATP synthesis coupled electron transport	6.10	17	5.49e-07
GO:BP	ribonucleoside triphosphate metabolic process	4.14	24	8.49e-07
GO:BP	generation of precursor metabolites and energy	2.77	40	1.13e-06
GO:BP	regulation of DNA replication	6.23	16	1.18e-06
GO:BP	DNA repair	2.39	51	1.44e-06
GO:BP	aerobic electron transport chain	5.97	16	2.15e-06
GO:BP	respiratory electron transport chain	4.99	18	4.43e-06
GO:BP	cellular response to stress	1.79	90	5.95e-06
GO:BP	ribosomal large subunit assembly	10.16	10	9.32e-06
GO:BP	maturation of 5.8S rRNA	6.79	13	1.21e-05
GO:BP	nucleoside triphosphate biosynthetic process	5.23	16	1.41e-05
GO:BP	energy derivation by oxidation of organic compounds	3.00	30	1.49e-05
GO:BP	ATP metabolic process	4.29	19	1.86e-05
GO:BP	mitochondrion organization	2.51	39	1.97e-05

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	purine ribonucleoside triphosphate metabolic process	3.88	21	2.09e-05
GO:BP	mRNA processing	2.50	39	2.09e-05
GO:BP	RNA localization	3.69	22	2.39e-05
GO:BP	regulation of DNA metabolic process	2.92	30	2.42e-05
GO:BP	tRNA metabolic process	2.81	31	3.49e-05
GO:BP	mRNA metabolic process	2.21	47	4.07e-05
GO:BP	purine nucleoside triphosphate metabolic process	3.69	21	4.37e-05
GO:BP	ribonucleoside triphosphate biosynthetic process	5.45	14	5.12e-05
GO:BP	nuclear transport	2.79	30	5.99e-05
GO:BP	nucleocytoplasmic transport	2.79	30	5.99e-05
GO:BP	'de novo' post-translational protein folding	8.31	10	6.05e-05
GO:BP	mitochondrial transport	3.47	22	6.14e-05
GO:BP	nucleobase-containing small molecule metabolic process	2.04	53	7.60e-05
GO:BP	maturation of SSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA)	6.27	12	8.09e-05
GO:BP	'de novo' protein folding	7.95	10	8.96e-05
GO:BP	cellular component organization or biogenesis	1.26	310	9.53e-05
GO:BP	nucleoside monophosphate biosynthetic process	5.12	14	9.79e-05
GO:BP	cell cycle checkpoint signaling	3.59	20	1.16e-04
GO:BP	regulation of cell cycle process	2.18	44	1.16e-04
GO:BP	RNA splicing	2.51	33	1.35e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	regulation of cell cycle	1.95	55	1.68e-04
GO:BP	nucleotide metabolic process	2.10	46	1.68e-04
GO:BP	translational initiation	5.78	12	1.79e-04
GO:BP	nucleobase-containing compound transport	3.22	22	1.83e-04
GO:BP	mRNA splicing, via spliceosome	2.70	28	2.22e-04
GO:BP	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile	2.70	28	2.22e-04
GO:BP	RNA splicing, via transesterification reactions	2.70	28	2.22e-04
GO:BP	nucleotide biosynthetic process	2.53	31	2.28e-04
GO:BP	protein maturation	2.16	42	2.32e-04
GO:BP	establishment of RNA localization	3.70	18	2.32e-04
GO:BP	mitochondrial transmembrane transport	3.70	18	2.32e-04
GO:BP	nucleic acid transport	3.70	18	2.32e-04
GO:BP	RNA transport	3.70	18	2.32e-04
GO:BP	nucleoside phosphate biosynthetic process	2.50	31	2.80e-04
GO:BP	nuclear export	3.33	20	3.06e-04
GO:BP	nucleoside monophosphate metabolic process	4.57	14	3.08e-04
GO:BP	chaperone cofactor-dependent protein refolding	7.84	9	3.37e-04
GO:BP	regulation of protein stability	3.41	19	3.76e-04
GO:BP	formation of cytoplasmic translation initiation complex	11.64	7	3.80e-04
GO:BP	cytoplasmic translational initiation	7.48	9	4.85e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	nucleoside phosphate metabolic process	2.00	46	4.85e-04
GO:BP	protein stabilization	3.85	16	4.94e-04
GO:BP	chromosome organization	2.15	38	6.51e-04
GO:BP	DNA integrity checkpoint signaling	3.75	16	6.72e-04
GO:BP	regulation of cell cycle phase transition	2.42	30	6.83e-04
GO:BP	ribose phosphate metabolic process	2.19	36	7.72e-04
GO:BP	ribonucleoside monophosphate biosynthetic process	4.88	12	8.23e-04
GO:BP	small molecule metabolic process	1.50	106	8.46e-04
GO:BP	response to stress	1.45	123	9.23e-04
GO:BP	proton motive force-driven ATP synthesis	6.86	9	9.28e-04
GO:BP	mitochondrial DNA metabolic process	9.85	7	1.15e-03
GO:BP	ATP biosynthetic process	6.58	9	1.26e-03
GO:BP	mitochondrial electron transport, NADH to ubiquinone	6.58	9	1.26e-03
GO:BP	viral gene expression	18.29	5	1.45e-03
GO:BP	chaperone-mediated protein folding	5.03	11	1.45e-03
GO:BP	purine ribonucleoside triphosphate biosynthetic process	5.03	11	1.45e-03
GO:BP	nuclear DNA replication	6.33	9	1.67e-03
GO:BP	cell cycle DNA replication	6.33	9	1.67e-03
GO:BP	purine nucleoside triphosphate biosynthetic process	4.91	11	1.78e-03
GO:BP	DNA strand elongation involved in DNA replication	7.32	8	1.93e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	ribose phosphate biosynthetic process	2.55	24	2.07e-03
GO:BP	ribonucleoside monophosphate metabolic process	4.39	12	2.07e-03
GO:BP	ribonucleotide metabolic process	2.12	34	2.14e-03
GO:BP	DNA strand elongation	6.97	8	2.67e-03
GO:BP	ribosomal small subunit assembly	8.54	7	2.70e-03
GO:BP	RNA export from nucleus	3.77	13	4.16e-03
GO:BP	DNA replication checkpoint signaling	6.36	8	5.00e-03
GO:BP	import into the mitochondrion	3.92	12	5.82e-03
GO:BP	rRNA modification	5.14	9	7.66e-03
GO:BP	positive regulation of signal transduction by p53 class mediator	13.06	5	8.24e-03
GO:BP	GMP biosynthetic process	9.15	6	8.32e-03
GO:BP	ribonucleotide biosynthetic process	2.42	22	8.55e-03
GO:BP	protein targeting to mitochondrion	3.66	12	1.06e-02
GO:BP	establishment of protein localization to organelle	1.91	35	1.13e-02
GO:BP	negative regulation of cell cycle phase transition	2.49	20	1.22e-02
GO:BP	'de novo' IMP biosynthetic process	11.43	5	1.51e-02
GO:BP	non-membrane-bounded organelle assembly	1.99	30	1.66e-02
GO:BP	negative regulation of cell cycle	2.19	24	1.71e-02
GO:BP	DNA replication initiation	5.23	8	1.71e-02
GO:BP	XMP biosynthetic process	18.29	4	1.71e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	'de novo' XMP biosynthetic process	18.29	4	1.71e-02
GO:BP	viral translation	18.29	4	1.71e-02
GO:BP	XMP metabolic process	18.29	4	1.71e-02
GO:BP	negative regulation of DNA metabolic process	3.43	12	1.71e-02
GO:BP	AMP biosynthetic process	7.84	6	1.71e-02
GO:BP	GMP metabolic process	7.84	6	1.71e-02
GO:BP	regulation of DNA-templated DNA replication	7.84	6	1.71e-02
GO:BP	mitochondrial genome maintenance	6.10	7	1.85e-02
GO:BP	regulation of signal transduction by p53 class mediator	6.10	7	1.85e-02
GO:BP	mitotic cell cycle	1.69	45	2.01e-02
GO:BP	mitotic cell cycle checkpoint signaling	3.13	13	2.10e-02
GO:BP	positive regulation of translation	3.59	11	2.11e-02
GO:BP	carbohydrate derivative biosynthetic process	1.64	49	2.14e-02
GO:BP	protein import into nucleus	2.80	15	2.20e-02
GO:BP	DNA geometric change	4.33	9	2.22e-02
GO:BP	'de novo' AMP biosynthetic process	10.16	5	2.26e-02
GO:BP	cellular component assembly	1.34	117	2.26e-02
GO:BP	double-strand break repair via break-induced replication	7.32	6	2.28e-02
GO:BP	immunoglobulin production involved in immunoglobulin-mediated immune response	5.82	7	2.28e-02
GO:BP	carbohydrate derivative metabolic process	1.49	69	2.28e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	negative regulation of cell cycle process	2.26	21	2.46e-02
GO:BP	purine ribonucleotide metabolic process	1.94	29	2.52e-02
GO:BP	maturation of LSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA)	5.57	7	2.86e-02
GO:BP	regulation of apoptotic signaling pathway	2.29	20	2.86e-02
GO:BP	tRNA aminoacylation	3.41	11	2.94e-02
GO:BP	regulation of G2/M transition of mitotic cell cycle	3.41	11	2.94e-02
GO:BP	protein localization to nucleus	2.49	17	3.01e-02
GO:BP	import into nucleus	2.69	15	3.01e-02
GO:BP	macromolecule methylation	2.81	14	3.04e-02
GO:BP	cell cycle	1.47	69	3.10e-02
GO:BP	regulation of translation	2.26	20	3.13e-02
GO:BP	telomere maintenance	3.35	11	3.13e-02
GO:BP	mitochondrial DNA replication	9.15	5	3.13e-02
GO:BP	somatic recombination of immunoglobulin genes involved in immune response	9.15	5	3.13e-02
GO:BP	somatic diversification of immunoglobulins involved in immune response	9.15	5	3.13e-02
GO:BP	isotype switching	9.15	5	3.13e-02
GO:BP	positive regulation of gene expression	1.74	37	3.13e-02
GO:BP	NADH dehydrogenase complex assembly	4.57	8	3.13e-02
GO:BP	mitochondrial respiratory chain complex I assembly	4.57	8	3.13e-02
GO:BP	purine nucleoside monophosphate biosynthetic process	4.57	8	3.13e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	purine ribonucleoside monophosphate biosynthetic process	4.57	8	3.13e-02
GO:BP	tRNA transport	14.63	4	3.24e-02
GO:BP	RNA modification	2.30	19	3.26e-02
GO:BP	establishment of protein localization to mitochondrion	3.09	12	3.30e-02
GO:BP	DNA recombination	2.07	23	3.64e-02
GO:BP	DNA-templated DNA replication maintenance of fidelity	4.43	8	3.69e-02
GO:BP	protein targeting	2.11	22	3.80e-02
GO:BP	amino acid activation	3.25	11	3.83e-02
GO:BP	protein localization to mitochondrion	3.01	12	4.05e-02
GO:BP	telomere organization	3.19	11	4.28e-02
GO:BP	translational elongation	4.30	8	4.31e-02
GO:BP	regulation of DNA strand elongation	8.31	5	4.39e-02
GO:BP	mitotic cell cycle process	1.71	36	4.39e-02
GO:BP	purine nucleotide metabolic process	1.76	33	4.40e-02
GO:BP	regulation of apoptotic process	1.58	46	4.77e-02
GO:BP	mitochondrial gene expression	2.93	12	4.86e-02
GO:BP	cell cycle process	1.50	57	4.88e-02
GO:BP	organelle organization	1.23	174	4.94e-02
Cellular Component				
GO:CC	ribonucleoprotein complex	5.28	181	7.13e-79

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	ribosome	8.45	100	9.07e-64
GO:CC	ribosomal subunit	9.31	90	8.18e-62
GO:CC	cytosolic ribosome	10.70	69	3.41e-52
GO:CC	intracellular anatomical structure	1.26	951	6.67e-51
GO:CC	membrane-enclosed lumen	2.62	271	6.67e-51
GO:CC	intracellular organelle lumen	2.62	271	6.67e-51
GO:CC	organelle lumen	2.62	271	6.67e-51
GO:CC	nucleolus	4.68	111	8.60e-42
GO:CC	intracellular organelle	1.33	823	1.15e-41
GO:CC	protein-containing complex	1.73	467	5.00e-40
GO:CC	organelle	1.30	829	4.21e-37
GO:CC	nuclear lumen	2.49	221	4.84e-37
GO:CC	intracellular membrane-bounded organelle	1.39	719	2.65e-36
GO:CC	non-membrane-bounded organelle	1.85	362	1.14e-34
GO:CC	intracellular non-membrane-bounded organelle	1.85	361	2.45e-34
GO:CC	large ribosomal subunit	8.79	52	1.03e-33
GO:CC	membrane-bounded organelle	1.34	729	1.48e-31
GO:CC	cytosolic large ribosomal subunit	10.51	40	1.85e-29
GO:CC	mitochondrion	2.46	177	2.97e-28
GO:CC	cytosol	2.09	237	4.82e-28

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	small ribosomal subunit	10.00	37	3.59e-26
GO:CC	nucleus	1.53	462	4.75e-26
GO:CC	preribosome	8.06	43	6.98e-26
GO:CC	cytosolic small ribosomal subunit	12.20	29	1.62e-23
GO:CC	cytoplasm	1.29	685	9.10e-22
GO:CC	mitochondrial protein-containing complex	4.57	55	9.42e-20
GO:CC	nuclear protein-containing complex	2.21	137	2.38e-17
GO:CC	organelle envelope	2.56	101	8.81e-17
GO:CC	small-subunit processome	8.20	26	1.78e-15
GO:CC	mitochondrial matrix	3.99	42	9.69e-13
GO:CC	nucleoplasm	1.94	133	3.47e-12
GO:CC	mitochondrial envelope	2.71	68	3.51e-12
GO:CC	mitochondrial inner membrane	3.34	50	3.51e-12
GO:CC	organelle inner membrane	3.14	54	4.23e-12
GO:CC	90S preribosome	8.05	20	1.61e-11
GO:CC	inner mitochondrial membrane protein complex	4.50	29	6.05e-10
GO:CC	mitochondrial membrane	2.58	60	8.01e-10
GO:CC	chromosome	1.98	91	1.20e-08
GO:CC	organellar ribosome	5.03	21	5.82e-08
GO:CC	mitochondrial ribosome	5.03	21	5.82e-08

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	catalytic complex	1.63	136	2.38e-07
GO:CC	translation preinitiation complex	13.10	9	1.03e-06
GO:CC	eukaryotic 48S preinitiation complex	15.14	8	1.98e-06
GO:CC	eukaryotic translation initiation factor 3 complex	12.17	9	2.20e-06
GO:CC	protein folding chaperone complex	7.33	12	4.35e-06
GO:CC	eukaryotic 43S preinitiation complex	12.62	8	1.11e-05
GO:CC	preribosome, large subunit precursor	8.60	10	1.27e-05
GO:CC	nuclear chromosome	3.03	25	3.48e-05
GO:CC	spliceosomal complex	2.63	29	8.28e-05
GO:CC	replication fork	4.82	13	1.51e-04
GO:CC	mitochondrial large ribosomal subunit	4.73	13	1.79e-04
GO:CC	organellar large ribosomal subunit	4.73	13	1.79e-04
GO:CC	nuclear envelope	2.30	34	1.90e-04
GO:CC	oxidoreductase complex	4.27	14	2.31e-04
GO:CC	protein-DNA complex	1.89	52	2.33e-04
GO:CC	U2-type spliceosomal complex	4.32	13	4.48e-04
GO:CC	sno(s)RNA-containing ribonucleoprotein complex	7.57	8	6.08e-04
GO:CC	mitochondrial proton-transporting ATP synthase complex	6.08	9	8.94e-04
GO:CC	proton-transporting ATP synthase complex	5.87	9	1.16e-03
GO:CC	Ctf18 RFC-like complex	15.77	5	1.30e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	catalytic step 2 spliceosome	3.40	14	2.49e-03
GO:CC	chaperonin-containing T-complex	7.36	7	2.67e-03
GO:CC	mitochondrial small ribosomal subunit	6.06	8	2.67e-03
GO:CC	organellar small ribosomal subunit	6.06	8	2.67e-03
GO:CC	Sm-like protein family complex	3.57	13	2.69e-03
GO:CC	nuclear pore	3.51	13	3.05e-03
GO:CC	respiratory chain complex	5.82	8	3.33e-03
GO:CC	spliceosomal snRNP complex	3.86	11	4.98e-03
GO:CC	mitochondrial intermembrane space	4.73	9	5.04e-03
GO:CC	respirasome	5.22	8	6.59e-03
GO:CC	small nuclear ribonucleoprotein complex	3.65	11	7.47e-03
GO:CC	organelle envelope lumen	4.37	9	8.53e-03
GO:CC	endopeptidase complex	3.11	13	8.59e-03
GO:CC	spliceosomal tri-snRNP complex	4.88	8	9.58e-03
GO:CC	proton-transporting ATP synthase complex, coupling factor F(o)	7.10	6	1.05e-02
GO:CC	preribosome, small subunit precursor	7.10	6	1.05e-02
GO:CC	peptidase complex	2.70	15	1.18e-02
GO:CC	DNA replication preinitiation complex	9.46	5	1.18e-02
GO:CC	eukaryotic translation initiation factor 3 complex, eIF3m	15.14	4	1.26e-02
GO:CC	U2-type prespliceosome	6.31	6	1.77e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	prespliceosome	6.31	6	1.77e-02
GO:CC	cytochrome complex	5.10	7	1.77e-02
GO:CC	fibrillar center	3.44	10	1.94e-02
GO:CC	chromatin	1.64	41	2.10e-02
GO:CC	Arp2/3 protein complex	7.89	5	2.33e-02
GO:CC	Ino80 complex	7.89	5	2.33e-02
GO:CC	nuclear membrane	2.38	16	2.43e-02
GO:CC	proton-transporting two-sector ATPase complex	3.26	10	2.66e-02
GO:CC	INO80-type complex	5.68	6	2.68e-02
GO:CC	MCM complex	7.28	5	3.08e-02
GO:CC	organelle membrane	1.25	140	3.13e-02
GO:CC	rough endoplasmic reticulum	3.88	8	3.13e-02
GO:CC	mitochondrial respirasome	5.16	6	3.92e-02
GO:CC	exosome (RNase complex)	5.16	6	3.92e-02
GO:CC	mitochondrial proton-transporting ATP synthase complex, coupling factor F(o)	6.76	5	3.92e-02
Molecular Function				
GO:MF	structural constituent of ribosome	9.21	88	5.28e-59
GO:MF	RNA binding	3.20	181	1.08e-43
GO:MF	nucleic acid binding	1.74	292	1.36e-21
GO:MF	structural molecule activity	2.69	109	8.75e-19

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:MF	organic cyclic compound binding	1.43	438	2.05e-17
GO:MF	rRNA binding	7.82	21	8.21e-11
GO:MF	translation regulator activity	4.84	29	8.60e-10
GO:MF	snoRNA binding	10.84	14	7.89e-09
GO:MF	translation factor activity, RNA binding	5.36	23	1.83e-08
GO:MF	translation regulator activity, nucleic acid binding	4.94	24	3.61e-08
GO:MF	unfolded protein binding	4.65	25	4.96e-08
GO:MF	catalytic activity, acting on a nucleic acid	2.13	71	3.41e-07
GO:MF	identical protein binding	2.09	58	2.05e-05
GO:MF	translation initiation factor activity	5.58	15	2.21e-05
GO:MF	ATP-dependent protein folding chaperone	4.92	15	1.11e-04
GO:MF	protein folding chaperone	4.01	17	2.99e-04
GO:MF	catalytic activity, acting on DNA	2.37	32	1.02e-03
GO:MF	mRNA binding	2.26	35	1.02e-03
GO:MF	DNA helicase activity	4.66	13	1.02e-03
GO:MF	catalytic activity, acting on RNA	2.07	41	1.27e-03
GO:MF	single-stranded DNA binding	3.64	16	1.61e-03
GO:MF	hydrolase activity, acting on acid anhydrides	1.66	71	1.87e-03
GO:MF	ribonucleoprotein complex binding	3.39	17	1.91e-03
GO:MF	oxidoreductase activity, acting on NAD(P)H, quinone or similar compound as acceptor	7.74	8	2.16e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:MF	pyrophosphatase activity	1.65	70	2.23e-03
GO:MF	hydrolase activity, acting on acid anhydrides, in phosphorus-containing anhydrides	1.64	70	2.65e-03
GO:MF	ribosome binding	3.99	13	3.66e-03
GO:MF	single-stranded DNA helicase activity	7.04	8	3.73e-03
GO:MF	oxidoreductase activity, acting on NAD(P)H	4.63	11	4.18e-03
GO:MF	ATP-dependent activity, acting on DNA	2.75	20	4.94e-03
GO:MF	helicase activity	2.66	21	4.94e-03
GO:MF	catalytic activity, acting on a tRNA	2.83	19	4.94e-03
GO:MF	translation elongation factor activity	7.53	7	7.78e-03
GO:MF	NADH dehydrogenase (ubiquinone) activity	9.68	6	7.91e-03
GO:MF	heat shock protein binding	3.45	13	1.17e-02
GO:MF	protein-folding chaperone binding	3.45	13	1.17e-02
GO:MF	oxidoreductase activity	1.55	68	1.17e-02
GO:MF	proton transmembrane transporter activity	2.79	17	1.23e-02
GO:MF	oxidoreduction-driven active transmembrane transporter activity	6.77	7	1.26e-02
GO:MF	ribonucleoside triphosphate phosphatase activity	1.57	61	1.65e-02
GO:MF	ATP hydrolysis activity	1.81	38	1.92e-02
GO:MF	electron transfer activity	5.16	8	2.07e-02
GO:MF	isomerase activity	2.25	21	3.26e-02
GO:MF	poly(U) RNA binding	9.68	5	3.33e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:MF	nucleotide binding	1.24	173	3.69e-02
GO:MF	nucleoside phosphate binding	1.24	173	3.69e-02
GO:MF	structural constituent of nuclear pore	5.42	7	3.82e-02
GO:MF	heterocyclic compound binding	1.23	180	4.54e-02

Table 3A: Gene ontology analysis of Significantly Upregulated DEGs identified at 24-hpi

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
Biological Process				
GO:BP	primary metabolic process	1.32	558	9.52e-14
GO:BP	protein metabolic process	1.48	313	1.04e-10
GO:BP	protein modification process	1.68	202	1.04e-10
GO:BP	macromolecule metabolic process	1.35	435	1.22e-10
GO:BP	organonitrogen compound metabolic process	1.39	381	1.64e-10
GO:BP	metabolic process	1.25	609	1.89e-10
GO:BP	macromolecule modification	1.62	212	2.68e-10
GO:BP	catabolic process	1.71	165	3.58e-09
GO:BP	secondary alcohol biosynthetic process	7.40	17	6.60e-08
GO:BP	transport	1.41	283	9.39e-08
GO:BP	establishment of localization	1.40	298	9.39e-08

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	sterol biosynthetic process	6.99	17	1.44e-07
GO:BP	macromolecule catabolic process	1.95	90	5.00e-07
GO:BP	localization	1.34	322	9.94e-07
GO:BP	organonitrogen compound catabolic process	1.84	100	1.01e-06
GO:BP	nitrogen compound transport	1.73	118	1.35e-06
GO:BP	protein catabolic process	2.07	71	2.36e-06
GO:BP	establishment of localization in cell	1.60	145	2.78e-06
GO:BP	cholesterol biosynthetic process	7.14	14	3.72e-06
GO:BP	regulation of catabolic process	2.09	66	5.48e-06
GO:BP	intracellular protein transport	2.03	69	6.74e-06
GO:BP	cellular metabolic process	1.25	422	7.24e-06
GO:BP	vesicle-mediated transport	1.66	119	8.14e-06
GO:BP	intracellular transport	1.66	118	8.14e-06
GO:BP	cellular localization	1.44	196	1.35e-05
GO:BP	ERAD pathway	6.28	14	1.77e-05
GO:BP	phytosteroid metabolic process	9.86	10	1.77e-05
GO:BP	phytosteroid biosynthetic process	9.86	10	1.77e-05
GO:BP	cellular response to stress	1.69	105	1.87e-05
GO:BP	negative regulation of gene expression	2.15	54	3.27e-05
GO:BP	macromolecule localization	1.48	162	4.06e-05

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	peptidyl-amino acid modification	2.40	42	4.49e-05
GO:BP	heparan sulfate proteoglycan biosynthetic process	7.75	11	5.17e-05
GO:BP	proteolysis involved in protein catabolic process	1.97	63	5.57e-05
GO:BP	proteasomal protein catabolic process	2.36	42	6.24e-05
GO:BP	regulation of metabolic process	1.27	329	6.35e-05
GO:BP	protein localization	1.51	135	1.30e-04
GO:BP	cellular macromolecule localization	1.51	135	1.34e-04
GO:BP	negative regulation of cellular metabolic process	1.64	99	1.56e-04
GO:BP	positive regulation of catabolic process	2.38	38	1.68e-04
GO:BP	steroid biosynthetic process	3.65	20	1.68e-04
GO:BP	intracellular pH reduction	6.12	12	1.68e-04
GO:BP	establishment of protein localization	1.63	100	1.68e-04
GO:BP	negative regulation of cellular process	1.37	203	1.70e-04
GO:BP	response to endoplasmic reticulum stress	3.24	23	1.76e-04
GO:BP	ergosterol metabolic process	10.76	8	1.76e-04
GO:BP	ergosterol biosynthetic process	10.76	8	1.76e-04
GO:BP	negative regulation of intracellular signal transduction	2.24	41	2.58e-04
GO:BP	alcohol biosynthetic process	3.22	22	3.23e-04
GO:BP	negative regulation of metabolic process	1.55	112	3.27e-04
GO:BP	sterol metabolic process	3.60	19	3.27e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	regulation of intracellular signal transduction	1.60	99	3.58e-04
GO:BP	post-translational protein modification	1.73	75	4.24e-04
GO:BP	protein modification by small protein conjugation or removal	1.73	73	5.68e-04
GO:BP	negative regulation of biological process	1.33	216	5.68e-04
GO:BP	protein phosphorylation	1.80	64	5.84e-04
GO:BP	response to chemical	1.49	123	6.61e-04
GO:BP	response to stress	1.42	149	8.20e-04
GO:BP	secondary alcohol metabolic process	3.50	18	8.20e-04
GO:BP	protein transport	1.62	86	8.20e-04
GO:BP	regulation of cellular metabolic process	1.26	290	8.57e-04
GO:BP	cellular catabolic process	1.76	64	1.02e-03
GO:BP	vacuolar acidification	6.16	10	1.18e-03
GO:BP	cellular lipid metabolic process	1.60	87	1.20e-03
GO:BP	regulation of signal transduction	1.41	146	1.27e-03
GO:BP	cholesterol metabolic process	3.70	16	1.34e-03
GO:BP	regulation of protein metabolic process	1.60	85	1.41e-03
GO:BP	regulation of cellular pH	3.19	19	1.47e-03
GO:BP	lipid metabolic process	1.50	105	1.77e-03
GO:BP	cellular lipid biosynthetic process	7.89	8	1.81e-03
GO:BP	regulation of response to stress	1.78	58	1.81e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	ubiquitin-dependent protein catabolic process	1.89	49	1.89e-03
GO:BP	regulation of cytokine production	2.27	32	2.03e-03
GO:BP	regulation of protein catabolic process	2.47	27	2.19e-03
GO:BP	regulation of response to stimulus	1.34	179	2.19e-03
GO:BP	proteoglycan metabolic process	3.70	15	2.31e-03
GO:BP	lipid biosynthetic process	1.77	57	2.31e-03
GO:BP	positive regulation of biological process	1.26	249	2.53e-03
GO:BP	negative regulation of cellular biosynthetic process	1.57	83	2.79e-03
GO:BP	regulation of intracellular pH	3.13	18	2.85e-03
GO:BP	modification-dependent protein catabolic process	1.84	49	2.99e-03
GO:BP	regulation of pH	2.99	19	3.08e-03
GO:BP	modification-dependent macromolecule catabolic process	1.84	49	3.12e-03
GO:BP	response to organonitrogen compound	2.06	37	3.12e-03
GO:BP	positive regulation of signal transduction	1.64	70	3.22e-03
GO:BP	negative regulation of biosynthetic process	1.56	83	3.32e-03
GO:BP	positive regulation of metabolic process	1.38	142	3.34e-03
GO:BP	peptidyl-threonine modification	5.28	10	3.48e-03
GO:BP	autophagy	2.33	28	3.55e-03
GO:BP	process utilizing autophagic mechanism	2.33	28	3.55e-03
GO:BP	homeostatic process	1.60	73	3.78e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	regulation of macromolecule metabolic process	1.22	291	3.83e-03
GO:BP	protein folding	2.40	26	3.87e-03
GO:BP	steroid metabolic process	2.50	24	4.19e-03
GO:BP	proteoglycan biosynthetic process	3.85	13	4.99e-03
GO:BP	response to nitrogen compound	1.93	40	5.15e-03
GO:BP	organic hydroxy compound biosynthetic process	2.48	23	6.55e-03
GO:BP	proteolysis	1.45	101	6.55e-03
GO:BP	regulation of proteolysis involved in protein catabolic process	2.78	19	6.74e-03
GO:BP	vacuolar transport	2.47	23	7.10e-03
GO:BP	regulation of cell communication	1.33	158	7.93e-03
GO:BP	establishment of protein localization to organelle	1.85	42	7.96e-03
GO:BP	negative regulation of macromolecule biosynthetic process	1.53	79	8.47e-03
GO:BP	glycoprotein metabolic process	1.88	40	8.79e-03
GO:BP	intracellular signal transduction	1.39	119	8.90e-03
GO:BP	negative regulation of macromolecule metabolic process	1.45	97	9.56e-03
GO:BP	phosphorus metabolic process	1.31	160	9.82e-03
GO:BP	regulation of signaling	1.32	158	1.06e-02
GO:BP	sulfur compound biosynthetic process	2.75	18	1.13e-02
GO:BP	positive regulation of cell communication	1.53	74	1.13e-02
GO:BP	positive regulation of signaling	1.53	74	1.13e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	endocytosis	1.83	41	1.20e-02
GO:BP	phosphate-containing compound metabolic process	1.31	158	1.20e-02
GO:BP	regulation of autophagy	2.31	24	1.20e-02
GO:BP	positive regulation of cellular process	1.24	217	1.54e-02
GO:BP	regulation of apoptotic process	1.62	58	1.54e-02
GO:BP	carbohydrate derivative metabolic process	1.47	84	1.58e-02
GO:BP	cellular biosynthetic process	1.24	220	1.58e-02
GO:BP	response to topologically incorrect protein	3.00	15	1.61e-02
GO:BP	positive regulation of protein catabolic process	2.64	18	1.71e-02
GO:BP	biosynthetic process	1.21	252	1.72e-02
GO:BP	positive regulation of protein metabolic process	1.67	50	1.78e-02
GO:BP	positive regulation of apoptotic process	2.19	25	1.78e-02
GO:BP	regulation of lysosomal lumen pH	8.07	6	1.86e-02
GO:BP	cytosolic transport	2.78	16	2.09e-02
GO:BP	positive regulation of response to stimulus	1.43	90	2.09e-02
GO:BP	regulation of programmed cell death	1.58	59	2.12e-02
GO:BP	morphogenesis of embryonic epithelium	3.70	11	2.25e-02
GO:BP	small molecule biosynthetic process	1.72	44	2.28e-02
GO:BP	chemical homeostasis	1.61	54	2.28e-02
GO:BP	regulation of defense response	1.88	34	2.33e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	embryonic morphogenesis	2.03	28	2.34e-02
GO:BP	lysosomal lumen acidification	10.57	5	2.34e-02
GO:BP	protein modification by small protein conjugation	1.59	56	2.50e-02
GO:BP	negative regulation of cytokine production	3.15	13	2.50e-02
GO:BP	cell death	1.73	42	2.50e-02
GO:BP	programmed cell death	1.73	42	2.50e-02
GO:BP	intracellular monoatomic cation homeostasis	1.82	36	2.50e-02
GO:BP	regulation of primary metabolic process	1.20	262	2.50e-02
GO:BP	protein modification by small protein removal	2.51	18	2.60e-02
GO:BP	intracellular monoatomic ion homeostasis	1.82	36	2.63e-02
GO:BP	monoatomic ion homeostasis	1.75	40	2.65e-02
GO:BP	sulfur compound metabolic process	1.95	30	2.66e-02
GO:BP	embryonic epithelial tube formation	3.89	10	2.70e-02
GO:BP	regulation of cytoplasmic pattern recognition receptor signaling pathway	3.89	10	2.70e-02
GO:BP	positive regulation of programmed cell death	2.10	25	2.71e-02
GO:BP	monoatomic cation homeostasis	1.75	39	2.96e-02
GO:BP	positive regulation of macromolecule metabolic process	1.32	123	3.22e-02
GO:BP	epithelial tube formation	3.79	10	3.22e-02
GO:BP	regulation of cellular catabolic process	2.07	25	3.36e-02
GO:BP	tissue morphogenesis	2.10	24	3.43e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	protein ubiquitination	1.60	51	3.47e-02
GO:BP	protein maturation	1.70	41	3.55e-02
GO:BP	regulation of proteasomal protein catabolic process	2.60	16	3.55e-02
GO:BP	positive regulation of intracellular signal transduction	1.61	49	3.55e-02
GO:BP	chaperone-mediated protein folding	3.70	10	3.73e-02
GO:BP	cellular homeostasis	1.64	45	3.99e-02
GO:BP	macroautophagy	2.32	19	4.03e-02
GO:BP	neural tube formation	4.03	9	4.08e-02
GO:BP	phospholipid metabolic process	1.71	39	4.17e-02
GO:BP	protein export from nucleus	4.55	8	4.17e-02
GO:BP	protein localization to organelle	1.53	57	4.32e-02
GO:BP	vacuole organization	2.24	20	4.33e-02
GO:BP	protein localization to vacuole	2.76	14	4.39e-02
GO:BP	vesicle organization	1.89	29	4.52e-02
GO:BP	phosphorylation	1.42	79	4.67e-02
GO:BP	cellular response to topologically incorrect protein	2.87	13	4.82e-02
GO:BP	peptidyl-serine modification	2.87	13	4.82e-02
GO:BP	phospholipid biosynthetic process	2.03	24	4.91e-02
GO:BP	proteasome-mediated ubiquitin-dependent protein catabolic process	1.90	28	4.97e-02

Cellular Component

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	cytoplasm	1.30	827	6.20e-27
GO:CC	intracellular membrane-bounded organelle	1.30	805	3.83e-25
GO:CC	membrane-bounded organelle	1.26	822	4.43e-22
GO:CC	endomembrane system	1.68	315	1.99e-20
GO:CC	intracellular anatomical structure	1.16	1,043	5.44e-20
GO:CC	organelle membrane	1.82	244	1.57e-19
GO:CC	intracellular organelle	1.19	881	2.20e-16
GO:CC	organelle	1.17	893	9.33e-14
GO:CC	endoplasmic reticulum	1.88	145	8.54e-12
GO:CC	bounding membrane of organelle	1.89	141	1.37e-11
GO:CC	cytosol	1.58	214	4.32e-10
GO:CC	organelle subcompartment	1.93	111	1.94e-09
GO:CC	vacuole	2.48	64	2.52e-09
GO:CC	lysosome	2.62	52	2.58e-08
GO:CC	lytic vacuole	2.59	52	3.79e-08
GO:CC	organelle lumen	1.53	190	5.31e-08
GO:CC	intracellular organelle lumen	1.53	190	5.31e-08
GO:CC	membrane-enclosed lumen	1.53	190	5.31e-08
GO:CC	endoplasmic reticulum subcompartment	1.98	85	9.98e-08
GO:CC	nucleoplasm	1.67	137	9.98e-08

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	endoplasmic reticulum membrane	1.98	84	1.17e-07
GO:CC	nuclear outer membrane-endoplasmic reticulum membrane network	1.94	84	2.90e-07
GO:CC	nuclear lumen	1.55	164	4.35e-07
GO:CC	cytoplasmic vesicle	1.65	128	5.29e-07
GO:CC	vacuolar membrane	2.73	39	9.21e-07
GO:CC	intracellular vesicle	1.63	128	1.01e-06
GO:CC	nucleus	1.24	447	1.08e-06
GO:CC	lysosomal membrane	3.03	32	1.47e-06
GO:CC	lytic vacuole membrane	3.03	32	1.47e-06
GO:CC	vesicle	1.56	136	3.62e-06
GO:CC	Golgi apparatus	1.68	105	4.83e-06
GO:CC	vesicle membrane	1.94	66	9.55e-06
GO:CC	Golgi membrane	2.28	45	1.13e-05
GO:CC	endosome	1.81	71	3.79e-05
GO:CC	perinuclear region of cytoplasm	2.47	34	6.02e-05
GO:CC	cytoplasmic vesicle membrane	1.85	62	9.07e-05
GO:CC	endosome membrane	2.16	37	4.17e-04
GO:CC	coated vesicle	2.38	26	1.90e-03
GO:CC	membrane	1.12	612	2.43e-03
GO:CC	vacuolar proton-transporting V-type ATPase complex	6.33	8	2.95e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	cation-transporting ATPase complex	4.14	11	4.36e-03
GO:CC	ATPase dependent transmembrane transport complex	3.96	11	6.39e-03
GO:CC	intracellular protein-containing complex	1.47	79	1.13e-02
GO:CC	ATPase complex	2.46	19	1.18e-02
GO:CC	clathrin-coated vesicle	2.72	16	1.23e-02
GO:CC	membrane raft	2.69	16	1.35e-02
GO:CC	membrane microdomain	2.66	16	1.48e-02
GO:CC	early endosome	1.94	28	2.07e-02
GO:CC	Golgi cisterna	3.11	12	2.23e-02
GO:CC	proton-transporting V-type ATPase complex	4.52	8	2.23e-02
GO:CC	nuclear body	1.81	33	2.23e-02
GO:CC	catalytic complex	1.30	130	2.23e-02
GO:CC	nucleolus	1.62	46	2.25e-02
GO:CC	endocytic vesicle	2.26	18	3.61e-02
GO:CC	protein-containing complex	1.13	366	4.13e-02
GO:CC	Golgi apparatus subcompartment	1.83	28	4.19e-02
Molecular Function				
GO:MF	enzyme binding	1.95	120	2.10e-09
GO:MF	protein binding	1.24	551	4.61e-08
GO:MF	identical protein binding	2.17	75	2.02e-07

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:MF	misfolded protein binding	7.40	10	9.76e-04
GO:MF	catalytic activity	1.16	522	1.47e-03
GO:MF	kinase binding	2.08	45	1.47e-03
GO:MF	transferase activity	1.30	233	2.67e-03
GO:MF	catalytic activity, acting on a protein	1.28	230	4.88e-03
GO:MF	protein kinase binding	2.04	40	4.88e-03
GO:MF	acyltransferase activity	1.63	72	7.45e-03
GO:MF	binding	1.07	924	1.02e-02
GO:MF	manganese ion binding	4.71	10	2.12e-02
GO:MF	protein domain specific binding	2.12	28	3.51e-02
GO:MF	steroid binding	3.20	14	3.61e-02
GO:MF	lipid binding	1.57	62	4.54e-02
GO:MF	ubiquitin-like protein ligase binding	2.50	19	4.88e-02

Table 3B: Gene ontology analysis of Significantly Downregulated DEGs identified at 24-hpi

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
Biological Process				
GO:BP	translation	5.77	136	3.59e-65
GO:BP	gene expression	2.26	288	1.04e-39

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	metabolic process	1.43	761	3.14e-36
GO:BP	organonitrogen compound biosynthetic process	2.54	213	1.45e-35
GO:BP	macromolecule biosynthetic process	2.03	319	5.47e-35
GO:BP	biosynthetic process	1.78	404	6.23e-33
GO:BP	cellular metabolic process	1.55	571	2.12e-32
GO:BP	nucleobase-containing compound metabolic process	1.99	308	3.62e-32
GO:BP	primary metabolic process	1.45	670	5.01e-32
GO:BP	cellular biosynthetic process	1.83	356	7.55e-31
GO:BP	macromolecule metabolic process	1.54	540	3.53e-29
GO:BP	nucleic acid metabolic process	2.02	241	3.92e-25
GO:BP	cytoplasmic translation	8.27	33	2.36e-20
GO:BP	ribonucleoprotein complex biogenesis	3.17	84	5.63e-19
GO:BP	cell cycle	2.28	145	5.63e-19
GO:BP	organonitrogen compound metabolic process	1.46	436	4.46e-17
GO:BP	aerobic respiration	5.33	41	7.30e-17
GO:BP	cell cycle process	2.35	121	1.51e-16
GO:BP	cellular respiration	4.93	43	2.46e-16
GO:BP	mitotic cell cycle	2.64	95	5.25e-16
GO:BP	oxidative phosphorylation	6.34	30	2.57e-14
GO:BP	protein-containing complex organization	1.97	153	5.98e-14

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	protein-RNA complex organization	4.20	41	8.95e-13
GO:BP	mitotic cell cycle process	2.68	76	9.49e-13
GO:BP	protein-RNA complex assembly	4.26	40	1.03e-12
GO:BP	electron transport chain	5.64	30	1.03e-12
GO:BP	RNA metabolic process	1.89	156	1.03e-12
GO:BP	generation of precursor metabolites and energy	3.07	60	1.49e-12
GO:BP	respiratory electron transport chain	5.74	28	5.17e-12
GO:BP	nucleobase-containing compound biosynthetic process	1.80	168	6.72e-12
GO:BP	ATP synthesis coupled electron transport	6.26	25	1.40e-11
GO:BP	DNA metabolic process	2.27	92	2.37e-11
GO:BP	mitochondrial ATP synthesis coupled electron transport	6.37	24	2.94e-11
GO:BP	energy derivation by oxidation of organic compounds	3.40	46	5.23e-11
GO:BP	ribosome biogenesis	2.90	58	5.23e-11
GO:BP	cellular component biogenesis	1.61	217	5.62e-11
GO:BP	aerobic electron transport chain	6.35	23	9.80e-11
GO:BP	protein-containing complex assembly	2.07	106	1.19e-10
GO:BP	cellular process	1.10	1,121	1.42e-10
GO:BP	protein metabolic process	1.41	327	6.60e-10
GO:BP	chromosome organization	2.47	59	2.36e-08
GO:BP	nucleic acid biosynthetic process	1.75	131	2.42e-08

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	amino acid metabolic process	2.61	52	4.48e-08
GO:BP	DNA repair	2.28	66	5.27e-08
GO:BP	tRNA aminoacylation	5.04	22	5.27e-08
GO:BP	DNA replication	3.29	35	9.38e-08
GO:BP	ribosome assembly	5.71	19	9.60e-08
GO:BP	DNA damage response	2.04	81	1.12e-07
GO:BP	amino acid activation	4.80	22	1.38e-07
GO:BP	regulation of cell cycle	2.05	78	2.06e-07
GO:BP	RNA processing	1.85	99	2.56e-07
GO:BP	cellular response to stress	1.74	118	2.81e-07
GO:BP	protein-DNA complex organization	2.23	62	3.95e-07
GO:BP	RNA biosynthetic process	1.71	122	4.31e-07
GO:BP	nucleoside triphosphate metabolic process	3.36	31	5.03e-07
GO:BP	tRNA aminoacylation for protein translation	4.92	20	5.03e-07
GO:BP	nuclear division	2.71	42	6.47e-07
GO:BP	cellular component assembly	1.51	179	8.36e-07
GO:BP	organelle organization	1.38	265	8.36e-07
GO:BP	DNA-templated DNA replication	3.44	29	8.52e-07
GO:BP	chromosome segregation	2.49	47	1.02e-06
GO:BP	non-membrane-bounded organelle assembly	2.40	49	1.65e-06

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	cellular component organization or biogenesis	1.25	417	3.54e-06
GO:BP	ATP metabolic process	3.84	23	4.27e-06
GO:BP	regulation of cell cycle process	2.13	58	5.99e-06
GO:BP	small molecule metabolic process	1.54	147	7.02e-06
GO:BP	cytoplasmic translational initiation	7.38	12	7.93e-06
GO:BP	ribonucleoside triphosphate metabolic process	3.32	26	1.07e-05
GO:BP	organelle fission	2.44	42	1.11e-05
GO:BP	translational initiation	5.34	15	1.59e-05
GO:BP	tricarboxylic acid cycle	5.34	15	1.59e-05
GO:BP	nucleoside triphosphate biosynthetic process	4.35	18	2.11e-05
GO:BP	ribosomal large subunit biogenesis	3.74	21	2.61e-05
GO:BP	purine nucleoside triphosphate metabolic process	3.25	25	2.63e-05
GO:BP	rRNA processing	2.56	36	2.63e-05
GO:BP	rRNA metabolic process	2.48	38	2.68e-05
GO:BP	nucleobase-containing small molecule metabolic process	1.91	67	2.86e-05
GO:BP	ribosomal small subunit biogenesis	3.69	21	3.07e-05
GO:BP	nucleotide metabolic process	2.00	59	3.40e-05
GO:BP	nucleoside phosphate metabolic process	1.96	61	3.63e-05
GO:BP	purine ribonucleoside triphosphate metabolic process	3.28	24	3.71e-05
GO:BP	chromatin organization	2.10	51	4.41e-05

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	ribose phosphate metabolic process	2.16	48	4.64e-05
GO:BP	carboxylic acid metabolic process	1.76	78	6.39e-05
GO:BP	protein-DNA complex assembly	3.28	23	6.53e-05
GO:BP	spindle organization	2.62	32	6.68e-05
GO:BP	oxoacid metabolic process	1.75	79	6.92e-05
GO:BP	regulation of cell cycle phase transition	2.32	39	8.76e-05
GO:BP	cell division	2.28	40	9.83e-05
GO:BP	mRNA metabolic process	1.95	56	1.28e-04
GO:BP	mRNA processing	2.14	45	1.28e-04
GO:BP	RNA splicing	2.25	40	1.31e-04
GO:BP	formation of cytoplasmic translation initiation complex	9.84	8	1.51e-04
GO:BP	RNA splicing, via transesterification reactions	2.42	34	1.68e-04
GO:BP	mRNA splicing, via spliceosome	2.42	34	1.68e-04
GO:BP	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile	2.42	34	1.68e-04
GO:BP	meiotic cell cycle process	2.71	28	1.68e-04
GO:BP	proton motive force-driven ATP synthesis	6.20	11	1.68e-04
GO:BP	organic acid metabolic process	1.70	80	1.79e-04
GO:BP	cell cycle checkpoint signaling	3.05	23	1.96e-04
GO:BP	nuclear chromosome segregation	2.47	32	2.06e-04
GO:BP	microtubule cytoskeleton organization involved in mitosis	2.67	28	2.13e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	ATP biosynthetic process	5.95	11	2.49e-04
GO:BP	response to stress	1.40	161	3.57e-04
GO:BP	ribonucleotide metabolic process	2.03	44	5.34e-04
GO:BP	tRNA metabolic process	2.28	34	5.83e-04
GO:BP	cellular component organization	1.20	381	8.36e-04
GO:BP	organelle assembly	1.63	79	8.36e-04
GO:BP	meiotic nuclear division	2.71	24	8.57e-04
GO:BP	translational elongation	4.77	12	8.57e-04
GO:BP	meiotic cell cycle	2.42	29	8.58e-04
GO:BP	L-amino acid metabolic process	2.46	28	9.12e-04
GO:BP	ribonucleoside triphosphate biosynthetic process	4.03	14	1.00e-03
GO:BP	purine ribonucleotide metabolic process	2.03	41	1.00e-03
GO:BP	purine nucleoside triphosphate biosynthetic process	4.29	13	1.08e-03
GO:BP	purine nucleotide metabolic process	1.90	48	1.11e-03
GO:BP	purine-containing compound metabolic process	1.86	50	1.20e-03
GO:BP	mitochondrial transport	2.68	23	1.42e-03
GO:BP	mitotic spindle organization	2.76	22	1.43e-03
GO:BP	sister chromatid segregation	2.91	20	1.62e-03
GO:BP	mitochondrial electron transport, NADH to ubiquinone	5.41	10	1.70e-03
GO:BP	chromatin remodeling	2.07	37	1.70e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	proteinogenic amino acid metabolic process	2.46	26	1.73e-03
GO:BP	regulation of mitotic cell cycle	2.05	37	1.99e-03
GO:BP	nucleoside phosphate biosynthetic process	2.09	35	2.32e-03
GO:BP	mitotic sister chromatid segregation	2.92	19	2.39e-03
GO:BP	mitotic nuclear division	2.82	20	2.41e-03
GO:BP	mitochondrial transmembrane transport	2.89	19	2.75e-03
GO:BP	regulation of G2/M transition of mitotic cell cycle	3.44	15	2.78e-03
GO:BP	mitochondrial translation	3.64	14	2.78e-03
GO:BP	DNA recombination	2.13	32	3.19e-03
GO:BP	fatty acid beta-oxidation	3.57	14	3.37e-03
GO:BP	mitochondrial gene expression	3.07	17	3.37e-03
GO:BP	double-strand break repair	2.15	31	3.48e-03
GO:BP	2'-deoxyribonucleotide biosynthetic process	7.89	7	3.48e-03
GO:BP	deoxyribose phosphate biosynthetic process	7.89	7	3.48e-03
GO:BP	regulation of cell cycle G2/M phase transition	3.18	16	3.60e-03
GO:BP	purine ribonucleoside triphosphate biosynthetic process	4.06	12	3.66e-03
GO:BP	nucleotide biosynthetic process	2.05	34	3.69e-03
GO:BP	mitotic cell cycle checkpoint signaling	3.03	17	3.78e-03
GO:BP	regulation of DNA replication	3.74	13	3.86e-03
GO:BP	protein peptidyl-prolyl isomerization	6.37	8	3.90e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	deoxyribonucleotide biosynthetic process	6.37	8	3.90e-03
GO:BP	sexual reproduction	1.74	51	4.56e-03
GO:BP	ribose phosphate biosynthetic process	2.20	28	5.00e-03
GO:BP	DNA integrity checkpoint signaling	2.95	17	5.00e-03
GO:BP	regulation of mitotic cell cycle phase transition	2.28	26	5.00e-03
GO:BP	alpha-amino acid metabolic process	2.16	29	5.33e-03
GO:BP	negative regulation of cell cycle phase transition	2.30	25	6.05e-03
GO:BP	regulation of cellular response to stress	2.09	30	6.75e-03
GO:BP	fatty acid oxidation	3.27	14	7.85e-03
GO:BP	lipid oxidation	3.21	14	9.33e-03
GO:BP	negative regulation of cell cycle process	2.15	27	9.53e-03
GO:BP	purine nucleoside diphosphate metabolic process	3.61	12	1.02e-02
GO:BP	negative regulation of cell cycle	2.03	30	1.10e-02
GO:BP	cell cycle DNA replication	4.68	9	1.22e-02
GO:BP	nuclear DNA replication	4.68	9	1.22e-02
GO:BP	regulation of chromosome segregation	3.10	14	1.27e-02
GO:BP	ribosomal small subunit assembly	6.31	7	1.33e-02
GO:BP	alpha-amino acid biosynthetic process	3.05	14	1.48e-02
GO:BP	peptidyl-proline modification	4.51	9	1.58e-02
GO:BP	mitochondrion organization	1.81	38	1.58e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	microtubule-based process	1.44	85	1.63e-02
GO:BP	glycolytic process	3.63	11	1.81e-02
GO:BP	regulation of DNA metabolic process	2.01	28	1.89e-02
GO:BP	import into the mitochondrion	3.14	13	1.89e-02
GO:BP	carbohydrate derivative metabolic process	1.42	89	1.91e-02
GO:BP	regulation of apoptotic signaling pathway	2.11	25	1.93e-02
GO:BP	centromere complex assembly	4.92	8	2.09e-02
GO:BP	ADP catabolic process	3.54	11	2.13e-02
GO:BP	regulation of mitotic metaphase/anaphase transition	3.87	10	2.13e-02
GO:BP	proteinogenic amino acid biosynthetic process	3.09	13	2.14e-02
GO:BP	L-amino acid biosynthetic process	3.09	13	2.14e-02
GO:BP	cellular component disassembly	2.06	26	2.14e-02
GO:BP	nucleoside diphosphate metabolic process	2.91	14	2.17e-02
GO:BP	formation of translation preinitiation complex	9.66	5	2.30e-02
GO:BP	positive regulation of signal transduction by p53 class mediator	9.66	5	2.30e-02
GO:BP	ribonucleoside diphosphate metabolic process	3.25	12	2.30e-02
GO:BP	nucleoside monophosphate biosynthetic process	3.25	12	2.30e-02
GO:BP	catabolic process	1.30	138	2.31e-02
GO:BP	pyruvate metabolic process	2.87	14	2.38e-02
GO:BP	mitotic cell cycle phase transition	2.87	14	2.38e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	purine nucleoside diphosphate catabolic process	3.46	11	2.38e-02
GO:BP	ADP metabolic process	3.46	11	2.38e-02
GO:BP	purine ribonucleoside diphosphate catabolic process	3.46	11	2.38e-02
GO:BP	pyridine nucleotide catabolic process	3.46	11	2.38e-02
GO:BP	regulation of metaphase/anaphase transition of cell cycle	3.76	10	2.42e-02
GO:BP	maturity of LSU-rRNA	3.76	10	2.42e-02
GO:BP	double-strand break repair via homologous recombination	2.29	20	2.53e-02
GO:BP	regulation of apoptotic process	1.53	60	2.68e-02
GO:BP	cell cycle phase transition	2.83	14	2.68e-02
GO:BP	GMP biosynthetic process	6.76	6	2.73e-02
GO:BP	ribonucleoside diphosphate catabolic process	3.38	11	2.75e-02
GO:BP	pyridine-containing compound catabolic process	3.38	11	2.75e-02
GO:BP	purine ribonucleoside diphosphate metabolic process	3.38	11	2.75e-02
GO:BP	ribonucleotide biosynthetic process	2.04	25	2.81e-02
GO:BP	nucleobase-containing compound catabolic process	1.84	32	2.83e-02
GO:BP	deoxyribonucleotide metabolic process	4.51	8	3.17e-02
GO:BP	cellular modified amino acid metabolic process	2.19	21	3.21e-02
GO:BP	2'-deoxyribonucleotide metabolic process	5.26	7	3.23e-02
GO:BP	recombinational repair	2.24	20	3.24e-02
GO:BP	purine ribonucleotide biosynthetic process	2.09	23	3.25e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	mitotic DNA integrity checkpoint signaling	3.06	12	3.38e-02
GO:BP	positive regulation of apoptotic process	2.00	25	3.42e-02
GO:BP	peptidyl-amino acid modification	1.78	34	3.42e-02
GO:BP	XMP metabolic process	13.53	4	3.42e-02
GO:BP	'de novo' XMP biosynthetic process	13.53	4	3.42e-02
GO:BP	XMP biosynthetic process	13.53	4	3.42e-02
GO:BP	mitochondrial electron transport, succinate to ubiquinone	13.53	4	3.42e-02
GO:BP	purine-containing compound biosynthetic process	1.93	27	3.50e-02
GO:BP	'de novo' IMP biosynthetic process	8.46	5	3.63e-02
GO:BP	purine nucleotide biosynthetic process	1.95	26	3.69e-02
GO:BP	tetrahydrofolate metabolic process	6.24	6	3.75e-02
GO:BP	regulation of mitotic sister chromatid separation	3.80	9	4.04e-02
GO:BP	regulation of translation	2.00	24	4.09e-02
GO:BP	deoxyribose phosphate metabolic process	4.98	7	4.10e-02
GO:BP	signal transduction in response to DNA damage	2.54	15	4.38e-02
GO:BP	macromolecule catabolic process	1.43	72	4.46e-02
GO:BP	meiosis I cell cycle process	2.43	16	4.50e-02
GO:BP	regulation of chromosome organization	2.35	17	4.54e-02
GO:BP	DNA-templated DNA replication maintenance of fidelity	3.69	9	4.84e-02
GO:BP	nucleoside monophosphate metabolic process	2.90	12	4.90e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:BP	regulation of double-strand break repair	2.90	12	4.90e-02
Cellular Component				
GO:CC	ribosome	6.68	108	4.42e-59
GO:CC	ribonucleoprotein complex	3.78	177	5.05e-54
GO:CC	ribosomal subunit	7.04	93	1.92e-53
GO:CC	cytosolic ribosome	8.63	76	4.32e-52
GO:CC	intracellular anatomical structure	1.23	1,265	8.08e-52
GO:CC	intracellular organelle	1.29	1,087	1.05e-42
GO:CC	organelle	1.26	1,100	9.05e-39
GO:CC	mitochondrion	2.39	235	6.18e-36
GO:CC	non-membrane-bounded organelle	1.72	460	2.54e-35
GO:CC	intracellular non-membrane-bounded organelle	1.72	459	4.71e-35
GO:CC	protein-containing complex	1.54	570	5.76e-32
GO:CC	cytosol	1.95	302	3.27e-30
GO:CC	cytosolic large ribosomal subunit	8.46	44	4.02e-29
GO:CC	cytoplasm	1.28	929	7.97e-28
GO:CC	membrane-enclosed lumen	1.94	275	3.97e-27
GO:CC	organelle lumen	1.94	275	3.97e-27
GO:CC	intracellular organelle lumen	1.94	275	3.97e-27
GO:CC	small ribosomal subunit	8.11	41	3.74e-26

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	large ribosomal subunit	6.31	51	3.76e-26
GO:CC	intracellular membrane-bounded organelle	1.28	905	4.52e-26
GO:CC	membrane-bounded organelle	1.26	933	9.54e-25
GO:CC	cytosolic small ribosomal subunit	9.54	31	1.85e-22
GO:CC	nuclear lumen	1.85	224	6.28e-19
GO:CC	nucleus	1.36	561	2.14e-17
GO:CC	mitochondrial protein-containing complex	3.58	59	2.73e-16
GO:CC	chromosome	2.09	131	2.56e-14
GO:CC	mitochondrial matrix	3.48	50	4.42e-13
GO:CC	nucleoplasm	1.80	169	1.02e-12
GO:CC	mitochondrial inner membrane	2.94	60	2.55e-12
GO:CC	organelle inner membrane	2.73	64	1.16e-11
GO:CC	catalytic complex	1.64	188	1.31e-10
GO:CC	nucleolus	2.34	76	1.62e-10
GO:CC	inner mitochondrial membrane protein complex	3.86	34	4.75e-10
GO:CC	organelle envelope	1.93	104	2.99e-09
GO:CC	mitochondrial envelope	2.13	73	3.18e-08
GO:CC	mitochondrial membrane	2.17	69	4.32e-08
GO:CC	chromosomal region	2.85	41	6.00e-08
GO:CC	chromosome, centromeric region	2.94	34	7.34e-07

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	nuclear protein-containing complex	1.60	136	7.62e-07
GO:CC	condensed chromosome	2.77	36	1.29e-06
GO:CC	mitochondrial proton-transporting ATP synthase complex	6.43	13	4.00e-06
GO:CC	oxidoreductase complex	4.24	19	4.39e-06
GO:CC	spindle	2.33	45	4.67e-06
GO:CC	proton-transporting ATP synthase complex	6.21	13	5.94e-06
GO:CC	mitochondrial small ribosomal subunit	6.65	12	8.40e-06
GO:CC	organellar small ribosomal subunit	6.65	12	8.40e-06
GO:CC	organellar ribosome	3.68	21	9.69e-06
GO:CC	mitochondrial ribosome	3.68	21	9.69e-06
GO:CC	translation preinitiation complex	9.59	9	1.15e-05
GO:CC	spliceosomal complex	2.45	37	1.52e-05
GO:CC	eukaryotic 48S preinitiation complex	11.08	8	1.63e-05
GO:CC	eukaryotic translation initiation factor 3 complex	8.90	9	2.36e-05
GO:CC	eukaryotic 43S preinitiation complex	9.23	8	9.12e-05
GO:CC	kinetochore	2.89	24	1.01e-04
GO:CC	respiratory chain complex	5.86	11	1.01e-04
GO:CC	cytochrome complex	5.86	11	1.01e-04
GO:CC	respirasome	5.25	11	3.03e-04
GO:CC	condensed chromosome, centromeric region	2.70	24	3.03e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	protein-DNA complex	1.72	65	3.03e-04
GO:CC	microtubule cytoskeleton	1.48	111	4.41e-04
GO:CC	U2-type spliceosomal complex	3.64	15	5.33e-04
GO:CC	small nuclear ribonucleoprotein complex	3.64	15	5.33e-04
GO:CC	centrosome	1.78	55	5.33e-04
GO:CC	proteasome core complex	6.23	9	5.43e-04
GO:CC	proton-transporting two-sector ATPase complex	3.58	15	6.27e-04
GO:CC	aminoacyl-tRNA synthetase multienzyme complex	8.08	7	1.12e-03
GO:CC	U4 snRNP	10.39	6	1.12e-03
GO:CC	mitochondrial respirasome	5.66	9	1.12e-03
GO:CC	spliceosomal snRNP complex	3.59	14	1.12e-03
GO:CC	Sm-like protein family complex	3.21	16	1.16e-03
GO:CC	preribosome	2.74	20	1.16e-03
GO:CC	chromatin	1.69	58	1.18e-03
GO:CC	catalytic step 2 spliceosome	3.02	17	1.37e-03
GO:CC	replication fork	3.53	13	2.44e-03
GO:CC	spliceosomal tri-snRNP complex	4.47	10	2.72e-03
GO:CC	U2 snRNP	5.54	8	3.72e-03
GO:CC	intracellular protein-containing complex	1.44	89	4.68e-03
GO:CC	U5 snRNP	7.55	6	6.68e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	piCln-Sm protein complex	9.89	5	8.41e-03
GO:CC	respiratory chain complex IV	5.70	7	9.06e-03
GO:CC	cleavage furrow	4.82	8	9.12e-03
GO:CC	Arp2/3 protein complex	6.92	6	1.02e-02
GO:CC	microtubule organizing center	1.54	60	1.02e-02
GO:CC	U1 snRNP	5.10	7	1.67e-02
GO:CC	mitochondrial proton-transporting ATP synthase complex, coupling factor F(o)	5.93	6	2.21e-02
GO:CC	U12-type spliceosomal complex	4.62	7	2.88e-02
GO:CC	eukaryotic translation initiation factor 3 complex, eIF3m	11.08	4	3.24e-02
GO:CC	small-subunit processome	2.77	12	3.26e-02
GO:CC	tricarboxylic acid cycle heteromeric enzyme complex	6.92	5	3.76e-02
GO:CC	nuclear chromosome	1.95	22	3.89e-02
GO:CC	proton-transporting ATP synthase complex, coupling factor F(o)	5.19	6	3.99e-02
GO:CC	mitotic spindle	2.16	17	4.58e-02
Molecular Function				
GO:MF	structural constituent of ribosome	7.30	95	1.45e-55
GO:MF	RNA binding	2.37	182	6.82e-26
GO:MF	structural molecule activity	2.26	125	1.73e-15
GO:MF	nucleic acid binding	1.49	340	2.94e-13
GO:MF	organic cyclic compound binding	1.30	544	9.27e-12

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:MF	rRNA binding	6.56	24	3.02e-11
GO:MF	translation regulator activity	3.92	32	1.15e-08
GO:MF	translation factor activity, RNA binding	4.28	25	2.61e-07
GO:MF	aminoacyl-tRNA ligase activity	5.08	20	5.57e-07
GO:MF	ligase activity, forming carbon-oxygen bonds	5.08	20	5.57e-07
GO:MF	translation regulator activity, nucleic acid binding	3.93	26	5.88e-07
GO:MF	ligase activity	2.63	45	6.96e-07
GO:MF	catalytic activity, acting on a nucleic acid	1.91	87	7.53e-07
GO:MF	catalytic activity, acting on a tRNA	3.17	29	8.40e-06
GO:MF	translation initiation factor activity	4.37	16	1.74e-04
GO:MF	oxidoreductase activity	1.61	96	3.56e-04
GO:MF	NAD binding	3.78	17	5.51e-04
GO:MF	identical protein binding	1.77	67	5.59e-04
GO:MF	catalytic activity, acting on RNA	1.89	51	1.40e-03
GO:MF	electron transfer activity	5.21	11	1.73e-03
GO:MF	mRNA binding	1.99	42	2.32e-03
GO:MF	catalytic activity, acting on DNA	2.07	38	2.37e-03
GO:MF	heterocyclic compound binding	1.24	247	8.80e-03
GO:MF	nucleoside phosphate binding	1.25	236	9.04e-03
GO:MF	nucleotide binding	1.25	236	9.04e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:MF	catalytic activity	1.13	553	9.04e-03
GO:MF	isomerase activity	2.20	28	9.04e-03
GO:MF	single-stranded DNA binding	2.84	17	1.33e-02
GO:MF	oxidoreductase activity, acting on NAD(P)H	3.71	12	1.38e-02
GO:MF	oxidoreductase activity, acting on NAD(P)H, quinone or similar compound as acceptor	5.69	8	1.42e-02
GO:MF	ATP-dependent activity, acting on DNA	2.32	23	1.60e-02
GO:MF	oxidoreductase activity, acting on the CH-NH group of donors, NAD or NADP as acceptor	6.63	7	1.60e-02
GO:MF	NAD+ binding	6.22	7	2.33e-02
GO:MF	proton transmembrane transporter activity	2.41	20	2.45e-02
GO:MF	binding	1.05	999	2.45e-02
GO:MF	translation elongation factor activity	5.53	7	4.38e-02

Table 4A: Significantly Enriched KEGG Pathways from DEGs identified at 12 and 24-hpi (Results from the DAVID online resource)

Time Point	Regulation	KEGG Term	DEG Count	Fold Enrichment	P-value (Adjusted)
12-hpi	down	Ribosome	80	6.68	3.16e-49
12-hpi	down	Oxidative phosphorylation	37	3.22	1.08e-08
12-hpi	down	DNA replication	18	6.01	1.09e-08
12-hpi	down	Ribosome biogenesis in eukaryotes	27	4.03	1.09e-08
12-hpi	down	Spliceosome	30	2.50	1.25e-04

Table 4A: Significantly Enriched KEGG Pathways from DEGs identified at 12 and 24-hpi (Results from the DAVID online resource)

Time Point	Regulation	KEGG Term	DEG Count	Fold Enrichment	P-value (Adjusted)
12-hpi	down	Nucleocytoplasmic transport	22	2.29	1.00e-02
12-hpi	down	Base excision repair	13	3.10	1.13e-02
12-hpi	down	Mismatch repair	9	4.29	1.13e-02
12-hpi	down	Nucleotide excision repair	14	2.86	1.29e-02
12-hpi	up	Steroid biosynthesis	10	6.14	1.65e-03
12-hpi	up	Autophagy - animal	29	2.34	2.12e-03
12-hpi	up	Cell cycle	27	2.30	3.90e-03
12-hpi	up	Influenza A	22	2.13	4.74e-02
24-hpi	down	Ribosome	88	5.54	2.81e-49
24-hpi	down	Oxidative phosphorylation	50	3.28	2.71e-13
24-hpi	down	Carbon metabolism	39	2.98	1.08e-08
24-hpi	down	Aminoacyl-tRNA biosynthesis	22	3.78	1.10e-06
24-hpi	down	Biosynthesis of amino acids	24	3.02	2.50e-05
24-hpi	down	Citrate cycle (TCA cycle)	15	4.36	2.50e-05
24-hpi	down	DNA replication	15	3.78	1.93e-04
24-hpi	down	Spliceosome	33	2.08	1.09e-03
24-hpi	down	Metabolic pathways	225	1.22	3.04e-03
24-hpi	down	Cell cycle	36	1.89	3.04e-03

Table 4A: Significantly Enriched KEGG Pathways from DEGs identified at 12 and 24-hpi (Results from the DAVID online resource)

Time Point	Regulation	KEGG Term	DEG Count	Fold Enrichment	P-value (Adjusted)
24-hpi	down	Propanoate metabolism	12	3.24	7.53e-03
24-hpi	down	Fatty acid degradation	14	2.86	7.77e-03
24-hpi	down	Glycolysis / Gluconeogenesis	17	2.42	1.19e-02
24-hpi	down	One carbon pool by folate	9	3.78	1.35e-02
24-hpi	down	Nucleotide excision repair	15	2.31	3.73e-02
24-hpi	down	Pyruvate metabolism	12	2.59	4.20e-02
24-hpi	up	Steroid biosynthesis	11	5.15	1.92e-03
24-hpi	up	Lysosome	29	2.24	3.94e-03
24-hpi	up	Terpenoid backbone biosynthesis	9	4.43	1.73e-02
24-hpi	up	Glycosaminoglycan biosynthesis - heparan sulfate / heparin	10	3.90	1.73e-02
24-hpi	up	Protein processing in endoplasmic reticulum	30	1.94	1.73e-02
24-hpi	up	Autophagy - animal	30	1.85	3.19e-02

Table 4B: Significantly Enriched KEGG Pathways from DEGs identified at 12 and 24-hpi (Results from the gprofiler2 R package)

Time Point	Regulation	KEGG Term	DEG Count	P-value (Adjusted)
12-hpi	down	Ribosome	35	7.70e-24
12-hpi	down	DNA replication	11	5.07e-07
12-hpi	down	Oxidative phosphorylation	19	3.10e-04

Table 4B: Significantly Enriched KEGG Pathways from DEGs identified at 12 and 24-hpi (Results from the gprofiler2 R package)

Time Point	Regulation	KEGG Term	DEG Count	P-value (Adjusted)
12-hpi	down	Base excision repair	9	1.15e-03
12-hpi	down	One carbon pool by folate	6	1.27e-03
12-hpi	down	Mismatch repair	6	3.49e-03
12-hpi	down	Ribosome biogenesis in eukaryotes	9	1.77e-02
12-hpi	down	Nucleotide excision repair	8	3.36e-02
12-hpi	up	Autophagy - animal	13	2.09e-02
24-hpi	down	Ribosome	41	4.71e-28
24-hpi	down	Aminoacyl-tRNA biosynthesis	12	3.04e-04
24-hpi	down	Oxidative phosphorylation	22	4.35e-04
24-hpi	down	Base excision repair	9	1.15e-02
24-hpi	down	Carbon metabolism	14	3.14e-02
24-hpi	down	Propanoate metabolism	6	3.99e-02
24-hpi	up	Ubiquitin mediated proteolysis	17	7.26e-03
24-hpi	up	Steroid biosynthesis	5	2.63e-02

³²⁹ **SUPPLEMENTARY INFORMATION/MATERIALS**