

1      Turkey B-cell Transcriptome Profile During THEV Infection

2      Highlights Upregulated Cell Death and Breakdown Pathways

3      That May Mediate Immunosuppression

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15

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). THEV is transmitted via the fecal-oral route and 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). Naturally-occurring low pathogenic (avirulent) strains of THEV have been isolated, which  
26 show subclinical infections but retain the immunosuppressive effects. Since its isolation from a pheasant  
27 spleen, the Virginia Avirulent Strain (VAS) has been used effectively as a live vaccine despite the immuno-  
28 suppressive side-effects, but the vaccinated birds are rendered more susceptible to opportunistic infections  
29 and death than 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 of  
32 B-cells (specifically, IgM+ B-cells) and macrophages ensue along with increased T-cell counts with abnormal  
33 T-cell subpopulation (CD4+ and CD8+) ratios. The cell death seen in the infected 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). Immunopathogenesis via cytokines from T-cells and macrophages has also  
36 been suggested as a mechanism of apoptosis leading to IMS. It is thought that the virus replication in the  
37 spleen attracts T-cells and peripheral blood macrophages to the spleen where the T-cells are activated by  
38 cytokines from activated macrophages and vice versa. The activated T-cells undergo clonal expansion and  
39 secrete interferons: type I (IFN- $\alpha$  and IFN- $\beta$ ) and type II (IFN- $\gamma$ ) as well as tumor necrosis factor (TNF)  
40 while activated macrophages secrete interleukin 6 (IL-6), TNF, and nitric oxide (NO), an antiviral agent  
41 with immunosuppressive properties. These cytokines released by T-cells and macrophages (e.g., TNF) are  
42 pro-apoptotic and may also induce apoptosis in bystander splenocytes, exacerbating the already numer-  
43 ous apoptotic and necrotic splenocytes, culminating in IMS (8, 11) (see **Figure 1**). However, the precise  
44 molecular mechanisms of THEV-induced IMS or pathways involved are poorly understood (6). Elucidating  
45 the specific mechanisms and pathways of THEV-induced IMS is the most crucial step in THEV research as  
46 it will present a means of mitigating IMS.

47 Next generation sequencing (NGS) is a groundbreaking technology that has significantly enhanced our un-  
48 derstanding of DNA and RNA structure and function and facilitated exceptional advancements in all domains

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

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

68 **RESULTS**

69 **Sequencing Results**

70 To identify the host transcriptome profile during THEV infection, MDTC-RP19 cells were THEV-infected or  
71 mock-infected in triplicates or duplicates, respectively, and harvested at 4-, 12-, 24-, and 72-hours post in-  
72 fection (hpi). mRNAs extracted from mock- or THEV-infected cells were sequenced on the Illumina platform,  
73 yielding a total of **776.1** million raw reads (149 bp in length) across all samples (see **Table 1** for sequenc-  
74 ing statistics). After trimming low-quality reads, the remaining **742.8** million total paired-end trimmed reads  
75 (approximately, **34.7-47.9** million reads per sample) were mapped to the genome of *Meleagris gallopavo*  
76 obtained from the National Center for Biotechnology Information (NCBI). The percentage of reads mapping  
77 to the host genome across all samples ranged from **32.4** to **89.2%**. The fraction of reads mapping to the  
78 host genome decreased while those mapping to the virus genome increased over course of the infection  
79 as the virus infectious cycle progressed. Despite excellent quality scores at all time points (**Table 1**), DEGs  
80 identified at 4 and 72 hpi did not yield any results in the downstream functional enrichment analyses (GO  
81 term and KEGG pathway analysis) and they were excluded from all subsequent analyses. In the remaining  
82 12 and 24 hpi samples, a high correlation was observed between biological replicates (**Figure 2A** and **B**).

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

84 Gene expression levels were estimated with the StringTie software (19) in Fragments per kilobase of tran-  
85 script per million (FPKM) units. The analysis of DEGs was performed with the DESeq2 R package (20)  
86 which employs negative binomial distribution model for read count comparisons. Using a  $P_{\text{adjusted}}$ -value  
87 cutoff  $\leq 0.05$  as the inclusion criteria, **2,343** and **3,295** genes were identified as differentially expressed  
88 at 12-hpi and 24-hpi, respectively. The DEG analyses results at 12 and 24-hpi have been deposited in  
89 NCBI Gene Expression Omnibus (<http://www.ncbi.nlm.nih.gov/geo>) under accession number ### with files  
90 named ~file\_name12hpi and file\_name24hpi~, respectively. At 12-hpi, **1,079** genes were upregulated and  
91 **1,264** genes downregulated, whereas **1,512** genes were upregulated and **1,783** genes downregulated at  
92 24-hpi (**Figure 2C**, and **Figure 3A-C**). The log<sub>2</sub>fold-change(FC) values at 12-hpi ranged between **-1.4** and  
93 **+1.7** for **TMEM156** (Transmembrane Protein 156) and **LIPG** (Lipase G), respectively. At 24-hpi, the log<sub>2</sub>FC  
94 values ranged between **-2.0** and **+2.6** for **C1QTNF12** (C1q And TNF Related 12) and **KCNG1** (Potassium  
95 Voltage-Gated Channel Modifier Subfamily G Member 1), respectively.

96 **Functional Enrichment Analyses (GO and KEGG pathway Analyses)**

97 Gene ontology (GO) enrichment analysis was performed for 12- and 24-hpi DEGs with the DAVID (Database  
98 for Annotation, Visualization and Integrated Discovery; version 2021) online resource (21) and the gprofiler2

99 R package – version **0.2.3** (22), which output results in three GO categories – cellular components (CP), bi-  
100 ological processes (BP), and molecular functions (MF). Results with  $P_{adjusted}$ -value  $\leq 0.05$  were considered  
101 functionally enriched. The GO enrichment analyses results at 12-hpi and 24-hpi showed significant over-  
102 laps among all three GO categories. At both time points, cellular breakdown processes were upregulated  
103 while cellular maintenance processes and structures were downregulated in all three GO categories (**Table**  
104 **2A-B** and **Table 3A-B**).

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

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

129 KEGG pathway analysis on the DEGs was also performed using both the gprofiler2 R package (22) and the  
130 DAVID online resource. Both resources gave similar results, but the results from DAVID (**Table 4A**) included

more information than the gprofiler2 results (**Table 4B**). KEGG pathway analysis was congruent with the GO results, revealing that generally, cell maintenance and upkeep pathways were downregulated while cell death and breakdown pathways were upregulated. Cell maintenance pathways such as DNA replication and repair, ribosome biogenesis, spliceosome, and oxidative phosphorylation were downregulated at both 12- and 24-hpi. Pathways such as: autophagy, response to virus (Influenza A), and steroid biosynthesis were upregulated at 12-hpi similar to 24-hpi, where pathways such as: autophagy, ubiquitin-mediated proteolysis, lysosome, protein processing in endoplasmic reticulum, and steroid biosynthesis were upregulated.

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

#### Cell Death and Breakdown Pathways Upregulated by THEV

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

163 *BNIP3*, *BMF*, *RB1CC1*, *ATF4*, *PDCD4*, and *APAF1*) and extrinsic (*FAS*, *FADD*, *TNFRSF1B*, *MADD*, and  
164 *RIPK1*) apoptotic pathways were represented. Conversely, several anti-apoptotic proteins such as *BCL2*  
165 apoptosis regulator (*BCL2*), *BCL2* interacting protein 2 (*BNIP2*; interacts directly with adenovirus E1B-19K  
166 protein), *BCL2* related protein A1 (*BCL2A1*), and apoptosis inhibitor 5 (*API5*) were also upregulated. Thus,  
167 apoptosis and its regulation pathways are clearly upregulated; this highlights the host-virus tug-of-war and  
168 underscores the ability of adenoviruses to trigger both apoptotic and anti-apoptotic pathways as seen in  
169 Mastadenoviruses. Moreover, several genes associated with autophagy such as: TNF receptor associated  
170 factor 6 (*TRAF6*), autophagy related 9A (*ATG9A*), unc-51 like autophagy activating kinase 2 (*ULK2*), and  
171 autophagy related 4B cysteine peptidase (*ATG4B*) were upregulated.

## 172 **Cell Cycle and Cell Maintenance Pathway Regulation Impacting Apoptosis**

173 Forcibly transitioning of the host cell cycle to the S phase during the early phase of infection is a prereq-  
174 uisite for a productive adenovirus infection. Interaction of the viral E1A early proteins with the host pRb  
175 (retinoblastoma) protein releases the host transcription factor E2F, which activates genes required for S  
176 phase cell cycle induction. Viral E1A also binds the host transcriptional co-activator p300/CBP (29). Our GO  
177 and KEGG pathway results showed that at 12 hpi, several key genes involved with cell cycle transition were  
178 upregulated. Notably, E1A binding protein p300 (*EP300*), cyclin genes (*CCND3*, *CCNG1*, *CCNG2*, *CDK6*),  
179 anaphase promoting complex subunit 1 (*ANAPC1*), and cell division cycle 27 (*CDC27*) were upregulated.  
180 However, unlike observed in Mastadenoviruses, the cell cycle regulation at 12 hpi seems complicated as  
181 some key cell cycle related genes as well as DNA and RNA synthesis, repair, metabolism, processing, and  
182 replication were concurrently downregulated. At 24 hpi, our KEGG pathway and GO analysis show that cell  
183 cycle was unanimously downregulated.

184 We found that several essential cell maintenance processes whose suppression can trigger apoptosis,  
185 were downregulated. Severe DNA damage is a known mechanism of apoptosis induction, called DNA  
186 damage-dependent apoptosis (30). Repression of RNA and protein synthesis is also strongly associated  
187 with apoptosis (31). Several processes related to DNA and RNA synthesis, maintenance, and repair such  
188 as nucleotide biosynthesis and metabolism, double strand break repair, DNA excision repair, RNA biosyn-  
189 thesis, RNA processing, DNA replication, mitotic cell cycle process, protein-RNA complex organization, and  
190 DNA damage response were downregulated. Notable genes identified include DNA ligase 1 (*LIG1*), X-ray  
191 repair cross complementing 1 (*XRCC1*), cyclin dependent kinase 1 and 2 (*CDK1*, *CDK2*), checkpoint kinase  
192 1 (*CHEK1*), 8-oxoguanine DNA glycosylase (*OGG1*), BLM RecQ-like-helicase (*BLM*), BRCA1 DNA repair  
193 associated (*BRCA1*), and several RAD family proteins (*RAD21*, *RAD51*, *RAD51B*, *RAD51C*, *RAD54B*). Ad-  
194 ditionally, protein-related processes, including ribosome biogenesis, rRNA processing, ribosome assembly,

195 protein folding, translational initiation, protein maturation, ribosome and ribonucleoprotein complex forma-  
196 tion, translation pre-initiation complex formation, and cytoplasmic translation were significantly downregu-  
197 lated. Notable genes identified include eukaryotic translation initiation factors (*EIF1*, *EIF1AX*, *EIF3E* and  
198 *EIF3F*, *EIF3H*, *EIF3I*, *EIF3L* and *EIF3M*), biogenesis of ribosomes BRX1 (*BRIX1*), MCTS1 re-initiation and  
199 release factor (*MCTS1*), and ribosomal protein subunits (*RPL8*, *RPL10a*, *RPL11*, *RP12*, *RP13*, *RP14*,  
200 *RP15*, *RP18a*, *RP19*). We speculate that these may all contribute to cell death via apoptosis; hence,  
201 THEV-induce IMS.

## 202 **Endoplasmic Reticulum (ER)-related Protein Degradation Response during THEV infection**

203 The KEGG pathway analysis (**Table 4A**) show that protein processing in the ER and ubiquitin-mediated pro-  
204 teolysis are significantly upregulated. The GO results (**Table 3A**) shows that specifically, the ER-associated  
205 protein degradation (ERAD) pathway was upregulated during THEV infection. The ER is the major site  
206 for protein synthesis, folding and quality control, and sorting. It is also harbors proteins and protein com-  
207 plexes necessary for other cellular functions including innate immune signaling, and serves as the site for  
208 lipid biosynthesis (32). The ERAD pathway, a ubiquitin-proteasome-dependent pathway, is a protein quality  
209 control system primarily activated for degradation of unwanted byproducts of protein biogenesis, such as  
210 misfolded and unassembled/orphaned proteins (32). In our results, the THEV-infected samples showed  
211 significant increase in ERAD pathway effector proteins, such as valosin containing protein (*VCP*), ubiquitin  
212 recognition factor in ER associated degradation 1 (*UFD1*), ER degradation enhancing alpha-mannosidase  
213 like proteins 1 and 3 (*EDEM1*, *EDEM3*), cullin 1 (*CUL1*), and ubiquilin 1 (*UBQLN1*). Our KEGG pathway  
214 (**Table 4B**) and GO (**Figure 4B**) results indicate a significant upregulation of ubiquitin mediated proteoly-  
215 sis with other ubiquitination pathway proteins such as: ubiquitin conjugating enzymes (*UBE2J2*, *UBE2E3*,  
216 *UBE2Z*), ubiquitin protein ligases (*UBE3A*, *UBE3B*), NPL4 homolog ubiquitin recognition factor (*NPLOC4*),  
217 and ubiquitin like modifier activating enzyme 6 (*UBA6*) showing significant upregulation. Additionally, the  
218 heat shock family of chaperone proteins such as: DnaJ heat shock protein family (*HSP40*) members  
219 (*DNAJB11*, *DNAJB12*, *DNAJB2*, *DNAJC10*), heat shock protein family A (*HSP70*) members (*HSPA4L*,  
220 *HSPA5*, *HSPA8*), and heat shock protein 90 alpha family class A member 1 (*HSP90AA1*) were upregulated.  
221 Moreover, the KEGG pathway analysis (**Table 4A**) shows a significant upregulation in lysosome formation,  
222 lumen acidification, and lysosomal degradation, likely an indication of ER-to-lysosome-associated degrada-  
223 tion. Taken together, these results suggest that THEV infection triggers significant ER-associated protein  
224 degradation, which may contribute to cell death and IMS.

## 225 **Differentially Expressed of Cytokine and Cytokine Receptor-encoding genes**

226 Our KEGG pathway results showed that a pathway similar to immune response to influenza A infection was

227 upregulated at 12 hpi. Our GO analysis also identified terms such as regulation of lymphocyte activation  
228 and regulation of cytokine production as upregulated at both 12 and 24 hpi. Genes involved include IL18,  
229 IL2RB, IL4R, IL5RA, TNF receptor associated factors (*TRAF2*, *TRAF3*, *TRAF6*, *TRAF7*, *TRAFD1*), TNF re-  
230 ceptor superfamily members (*TNFRSF1B*, *TNFRSF8*, *TNFSF4*), interferon-induced with helicase C domain  
231 1 (*IFIH1*), interferon-induced double-stranded RNA-activated protein kinase (*PKR*), and *CD80*. In contrast,  
232 cytokine inhibitors such as suppressor of cytokine signaling (*SOCS3* and *SOCS5*) were also upregulated  
233 at both 12 and 24 hpi and immunoglobulin production and isotype switching GO terms were downregu-  
234 lated at 12 hpi. This inconsistency is likely and indicator of the struggle between the virus and its host.  
235 While several cytokines were regulated by THEV like in the proposed model of THEV immunopathogenesis  
236 (**Figure 1**), the expected cytokines (IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$  TNF, IL-6, and NO) were not significantly differen-  
237 tially expressed in our data. However, many of the identified differentially expressed cytokines () are positive  
238 regulators of apoptosis; therefore, they may play a role in THEV-induced IMS.

### 239 **Cellular Metabolism Changes During THEV Infection**

240 Many viruses, such as hepatitis C virus (HCV), human cytomegalovirus, influenza virus, and rhinovirus,  
241 have been documented to manipulate cellular metabolism processes to their advantage (16, 33). A com-  
242 mon consequence of infection by many viruses is to induce high glucose metabolism in host cells to provide  
243 energy for viral gene expression and replication. Adenoviruses typically upregulate energy metabolic path-  
244 ways such as glycolysis in host cells (34). However, our GO results indicated a downregulation in glycoly-  
245 sis, tricarboxylic acid cycle, oxidative phosphorylation, and ATP synthesis (**Table 2B**). Conversely, protein  
246 metabolism was significantly upregulated. These results may suggest that THEV infection may modulate  
247 cellular energy metabolism processes differently than other adenoviruses. Interestingly, some viruses such  
248 as HCV cause opposite metabolic effects at different times after infection (33); therefore, it is possible that  
249 THEV may have similar characteristics. Also, the host interferon (IFN) antiviral response potently reverses  
250 the metabolic reprogramming (such as increased energy metabolism) imposed by the virus as a mecha-  
251 nism of inhibiting viral replication (33); hence, the downregulation of energy metabolic processes may be  
252 a host response to THEV. ~~Further studies done with primary host cells would be required to confirm this~~  
253 ~~finding.~~

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

255 To validate the RNA-seq results, 12 DEGs (8 upregulated and 4 downregulated) were selected for RT-  
256 qPCR. The DEGs were representative of apoptosis (*APAF1*, *BMF*, *FADD*, *MADD*, and *PDCD4*), ERAD and  
257 ubiquitination (*VCP*, *UFD1*, *EDEM1*), and ribosome biosynthetic (*EIF3D*, *EIF3M*, *RPL8*, *RPL10A*) pathways.  
258 As shown in **Figure 5**, the RT-qPCR results corroborate the RNA-seq results, further reinforcing the validity

<sup>259</sup> of the RNA-seq transcriptomic profile results. According to our Student's T-test and Mann-Whitney U test,  
<sup>260</sup> the difference in gene expression levels in all the selected genes were statistically significant.

261 **DISCUSSION**

262 CCHFV is a BS<sub>L</sub>-4 pathogen threatening public health in about 50 countries of Asia, Africa, southern Eu-  
263 rope, and the Middle East (Nasirian, 2020). Elucidation of virus-host interactions is urgently needed for  
264 not only the understanding of the viral infection and pathogenesis but also the design of antiviral therapies.  
265 However, as one of the most dangerous human pathogens, experimental handling of live CCHFV is strictly  
266 restricted in high-containment laboratories, slowing down the virological studies including animal and cell in-  
267 fection model development and optimization (Hawman and Feldmann, 2018). HEK293 is a well-recognized  
268 human cell model derived from kidney and permissive to CCHFV infection (Foldes et al., 2020; Dai S. et al.,  
269 2021a). Moreover, clinical observations have shown that CCHFV has tropism to kidney tis- sue (Ardalan  
270 et al., 2006; Deveci et al., 2013; Khazaei et al., 2018; Foldes et al., 2020). Additionally, HEK293 is a most  
271 often chosen model for omics study because of its availability of annotated human omics data- bases to  
272 conduct gene identi cation and function assignment and ready validation of the omics results by further  
273 experimental analysis with it. Thus, we here establish a cellular transcriptome pro le of CCHFV

274 Protein degradation was more pronounced at the later stage of infection (24 hpi) Why use avirulent THEV?

275 In the proposed model of THEV immunopathogenesis (**Figure 1**), cytokines are key players. However, the  
276 primary cytokines (IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$  TNF, IL-6, and NO) were not significantly differentially expressed  
277 in our data. This may be due to: 1. B-cell culture does cannot simulate cell interactions which are key in  
278 the model -> Full onset of cytokine release require communication 2. Cytokines may not play a dominant  
279 role in THEV-induced IMS since TNF-blocking drug (thalidomide) only prevented intestinal disease not  
280 immunosuppression. 3. This RNA-seq shows apoptosis but not the key cytokines in the model. Non-  
281 cytokine mediate cell death?

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

291 Regulation of genes involved in the cell cycle during THEV infection seemed complicated at 12 hpi, since

<sup>292</sup> both positive and negative regulators were both up- or down-regulated.

293 **CONCLUSIONS**

294 **MATERIALS AND METHODS**

295 **Cell culture and THEV Infection**

296 The Turkey B-cell line (MDTC-RP19, ATCC CRL-8135) was grown as a suspension culture in 1:1 complete  
297 Leibovitz's L-15/McCoy's 5A medium with 10% fetal bovine serum (FBS), 20% chicken serum (ChS), 5%  
298 tryptose phosphate broth (TPB), and 1% antibiotic solution (100 U/mL Penicillin and 100 $\mu$ g/mL Strepto-  
299 mycin), at 41°C in a humidified atmosphere with 5% CO<sub>2</sub>. Infected cells were maintained in 1:1 serum-  
300 reduced Leibovitz's L15/McCoy's 5A media (SRLM) with 2.5% FBS, 5% ChS, 1.2% TPB, and 1% antibiotic  
301 solution. A commercially available THEV vaccine was purchased from Hygieia Biological Labs (VAS strain).  
302 The stock virus was titrated using an in-house qPCR assay with titer expressed as genome copy number  
303 (GCN)/mL, similar to Mahshoub *et al* (35). Cells were THEV-infected or mock-infected in triplicates or du-  
304 plicates, respectively at a multiplicity of infection (MOI) of 100 GCN/cell, incubated at 41°C for 1 hour, and  
305 washed three times with phosphate buffered saline (PBS) to get rid of free virus particles. At each time point  
306 (4-, 12-, 24-, and 72-hpi), triplicate (THEV-infected) and duplicate (mock-infected) samples were harvested  
307 for total RNA extraction.

308 **RNA extraction and Sequencing**

309 Total RNA was extracted from infected cells using the Thermo Fisher RNaseous™-4PCR Total RNA Iso-  
310 lation Kit (which includes a DNase I digestion step) per manufacturer's instructions. An agarose gel elec-  
311 trophoresis was performed to check RNA integrity. The RNA quantity and purity was initially assessed using  
312 nanodrop, and RNA was used only if the A260/A280 ratio was 2.0 ± 0.05 and the A260/A230 ratio was >2  
313 and <2.2. Extracted total RNA samples were sent to LC Sciences, Houston TX for poly-A-tailed mRNA  
314 sequencing. RNA integrity was checked with Agilent Technologies 2100 Bioanalyzer High Sensitivity DNA  
315 Chip and poly(A) RNA-seq library was prepared following Illumina's TruSeq-stranded-mRNA sample prepa-  
316 ration protocol. Paired-end sequencing, generating 150 bp reads was performed on the Illumina NovaSeq  
317 6000 sequencing system. The paired-end 150bp sequences obtained during this study and all expression  
318 data have been submitted to the Gene Expression Omnibus database, under accession no #####

319 **Quality Control and Mapping Process**

320 Sequencing reads were processed following a well-established protocol described by Pertea *et al* (19),  
321 using Snakemake - version 7.32.4 (36), a popular workflow management system to drive the pipeline.  
322 Briefly, raw sequencing reads were trimmed with Cutadapt - version 1.10 (37) and the quality of trimmed

323 reads evaluated using the FastQC software, version 0.12.1 (Bioinformatics Group at the Babraham Institute,  
324 Cambridge, United Kingdom; [www.bioinformatics.babraham.ac.uk](http://www.bioinformatics.babraham.ac.uk)), achieving an overall Mean Sequence  
325 Quality (PHRED Score) of 36. Trimmed reads were mapped the reference *Meleagris gallopavo* genome file  
326 GCF\_000146605.3\_Turkey\_5.1\_genomic.fna.gz from NCBI ([https://ftp.ncbi.nlm.nih.gov/genomes/all/GCF/000/146/605/GCF\\_000146605.3\\_Turkey\\_5.1/](https://ftp.ncbi.nlm.nih.gov/genomes/all/GCF/000/146/605/GCF_000146605.3_Turkey_5.1/)) with Hisat2 - version 2.2.1 (19) using the accompanying  
327 gene transfer format (GTF) annotation file (GCF\_000146605.3\_Turkey\_5.1\_genomic.gtf.gz) to build a ge-  
328 nomic index. Samtools - version 1.19.2 was used to convert the output Sequence Alignment Map (SAM)  
329 file to the more manageable Binary Alignment Map (BAM) format. The StringTie (v2.2.1) software (19), set  
330 to expression estimation mode was used to generate normalized gene expression estimates from the BAM  
331 files for genes in the reference GTF file after which the prepDE.py3 script was used to extract read count  
332 information from the StringTie gene expression files, providing an expression-count matrix for downstream  
333 DEG analysis.

### 335 **DEG Analysis and Functional Enrichment Analysis**

336 DEG analysis between mock- and THEV-infected samples was performed using the very popular DE-  
337 Seq2 (20), which employs a Negative Binomial distribution model for read count comparisons. Genes  
338 with  $P_{\text{adjusted-value}} \leq 0.05$  were considered as differentially expressed. The sequencing data (FASTQ files)  
339 and read count data are deposited at NCBI Gene Expression Omnibus under accession number ###. The  
340 functional profiling of DEGs (GO and KEGG analyses) were performed based on GO databases and KEGG  
341 databases using DAVID and the R package gprofiler2 (22) with *Meleagris gallopavo* as the reference or-  
342 ganism. Results with  $P_{\text{adjusted-value}} \leq 0.05$  were included as functionally enriched. All visualization plots  
343 were made using ggplot2, pheatmap, and ggvenn R packages (38–40).

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

345 The gene expression levels of representative DEGs (*APAF1*, *BMF*, *FADD*, *PDCD4*, *MADD*, *VCP*, *UFD1*,  
346 *EDEM1*, *EIF3D*, *EIF3M*, *RPL8*, *RPL10A*) were validated by quantification of relative mRNA levels with  
347 turkey *GAPDH* mRNA levels as the control gene. Briefly, the samples were infected and RNA extracted as  
348 described for the RNA sequencing samples with three biological replicates at 12 and 24 hpi each for both  
349 THEV-infected or mock-infected samples. First-strand cDNA synthesis of total RNA was performed with an  
350 oligo-dT primer to amplify poly-A-tailed mRNA using SuperScript™ IV First-Strand Synthesis System. The  
351 parent RNA were digested using RNase H after cDNA synthesis was complete to ensure that only cDNA  
352 remain as the template for the RT-qPCR quantification. The RT-qPCR was performed with the PowerUp™

353 SYBR™ Green master mix from Applied Biosystems with primers designed manually in the SnapGene  
354 software. The primers were checked for specificity using NCBI Nucleotide BLAST (<https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastn>) before use. All primers used in this study are listed in **Supplementary**  
355  
356 **Table S3.** Relative mRNA levels were calculated by  $2^{-\Delta\Delta CT}$  method (41).

357 **Statistical Analysis**

358 Statistical analyses of the RT-qPCR results were performed using R (Version 4.3.3) with Student's t-test  
359 and Mann-Whitney U test for the comparison between two groups. A difference with P-value  $\leq 0.05$  was  
360 considered statistically significant.

361 **DATA AVAILABILITY**

362 The raw sequencing read data (FastQ), transcript expression counts, and total DEGs identified at 12 and 24  
363 hpi have been deposited at the NCBI Gene Expression Omnibus (<http://www.ncbi.nlm.nih.gov/geo>) under  
364 accession number #####.

365 **CODE AVAILABILITY**

- 366 All the code/scripts in the entire analysis pipeline are available on github (<https://github.com/Abraham->
- 367 Quaye/host\_rna\_seq)

368 **ACKNOWLEDGMENTS**

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370 high-performance computing systems to perform the memory-intensive steps in the analysis pipeline of this  
371 work.

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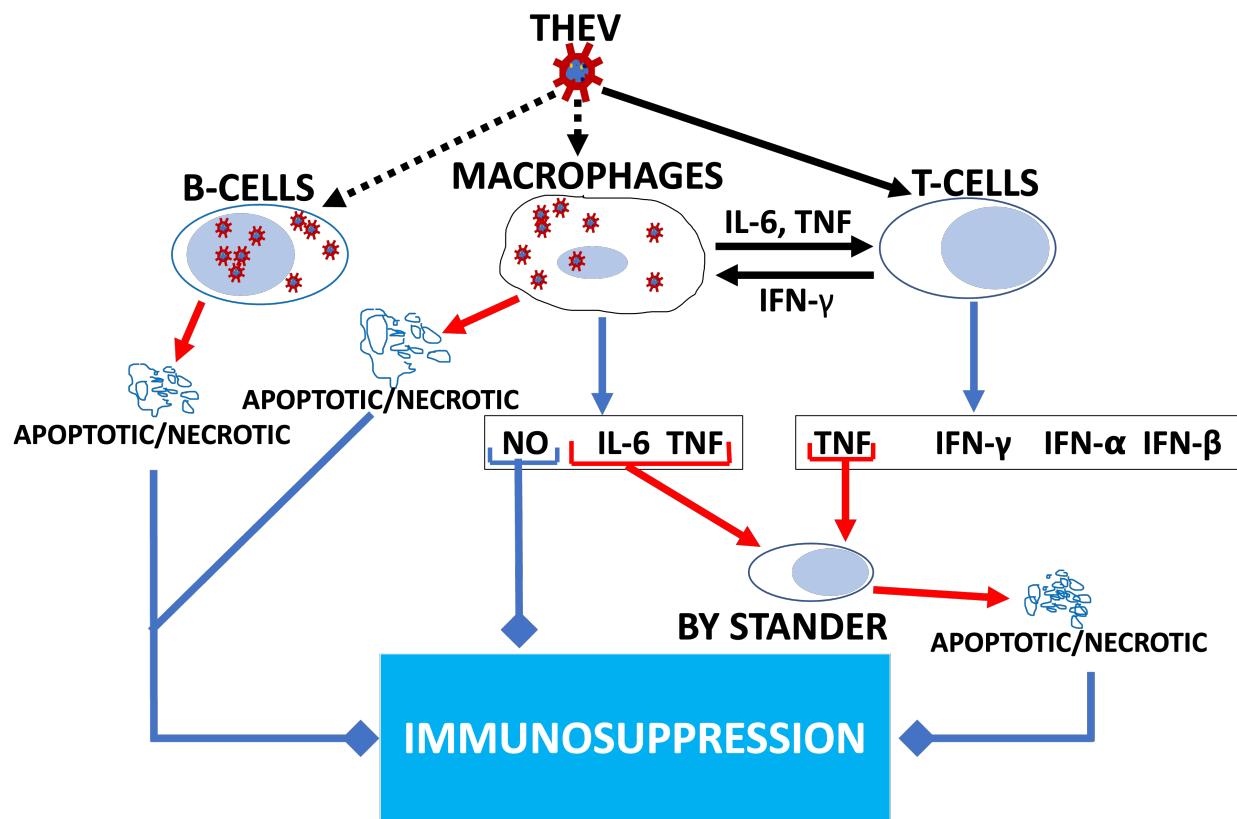
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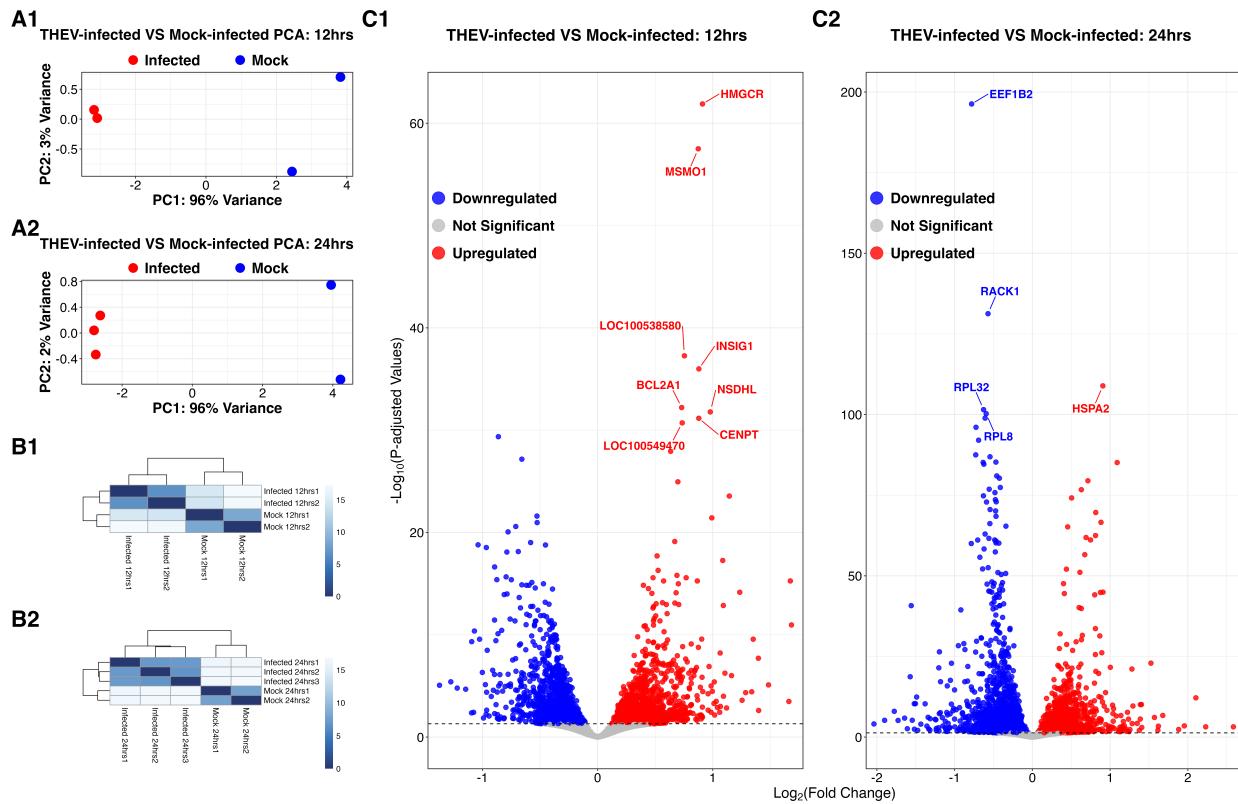
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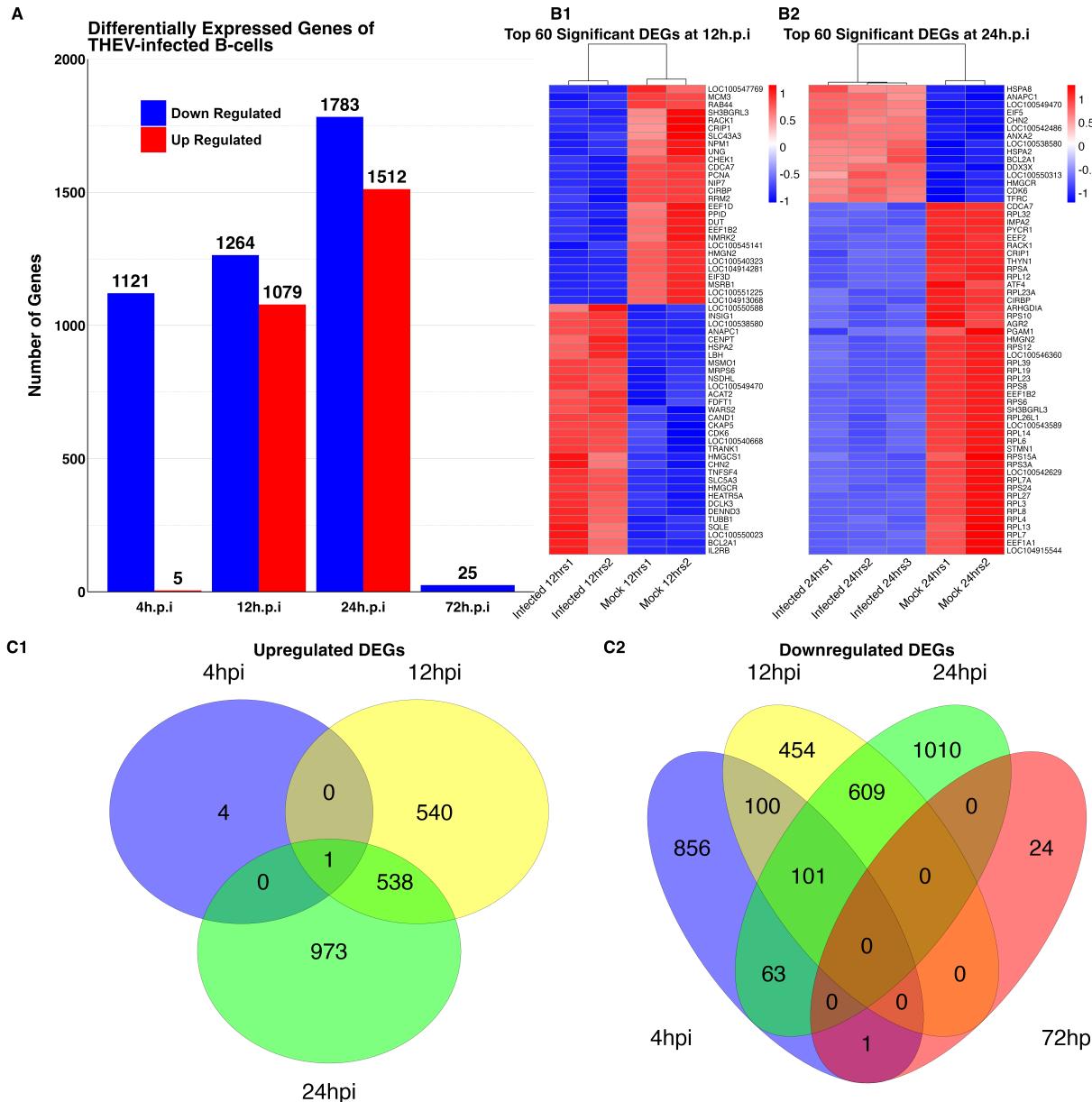
414 TABLES AND FIGURES



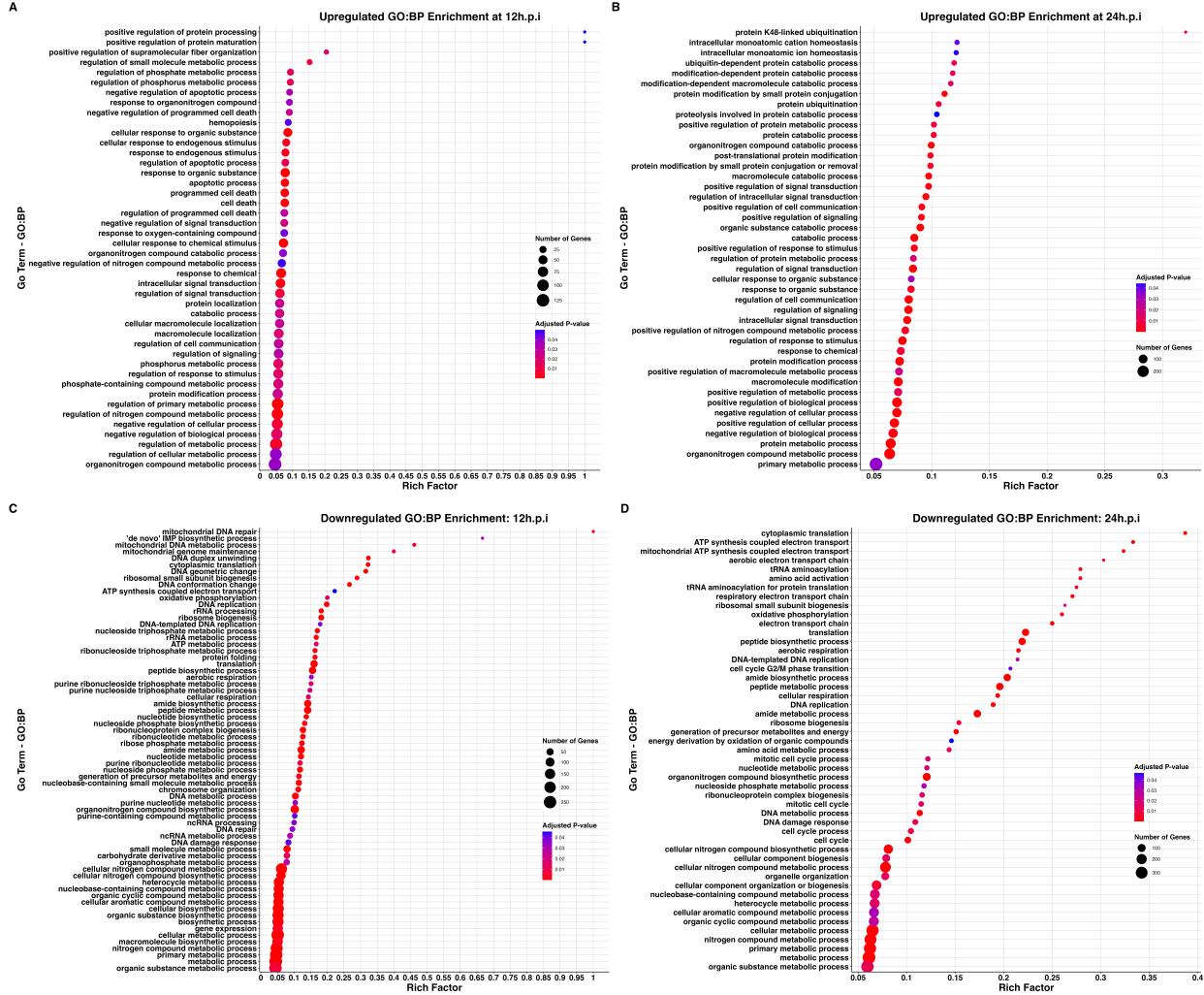
**Figure 1: Model of THEV-induced immunosuppression in turkeys.** THEV infection of target cells is indicated with black dotted arrows. Black unbroken arrows indicate cell activation. Red arrows indicate signals leading to apoptosis. Blue arrows indicate all cytokines released by the cell. Blue arrows 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**).

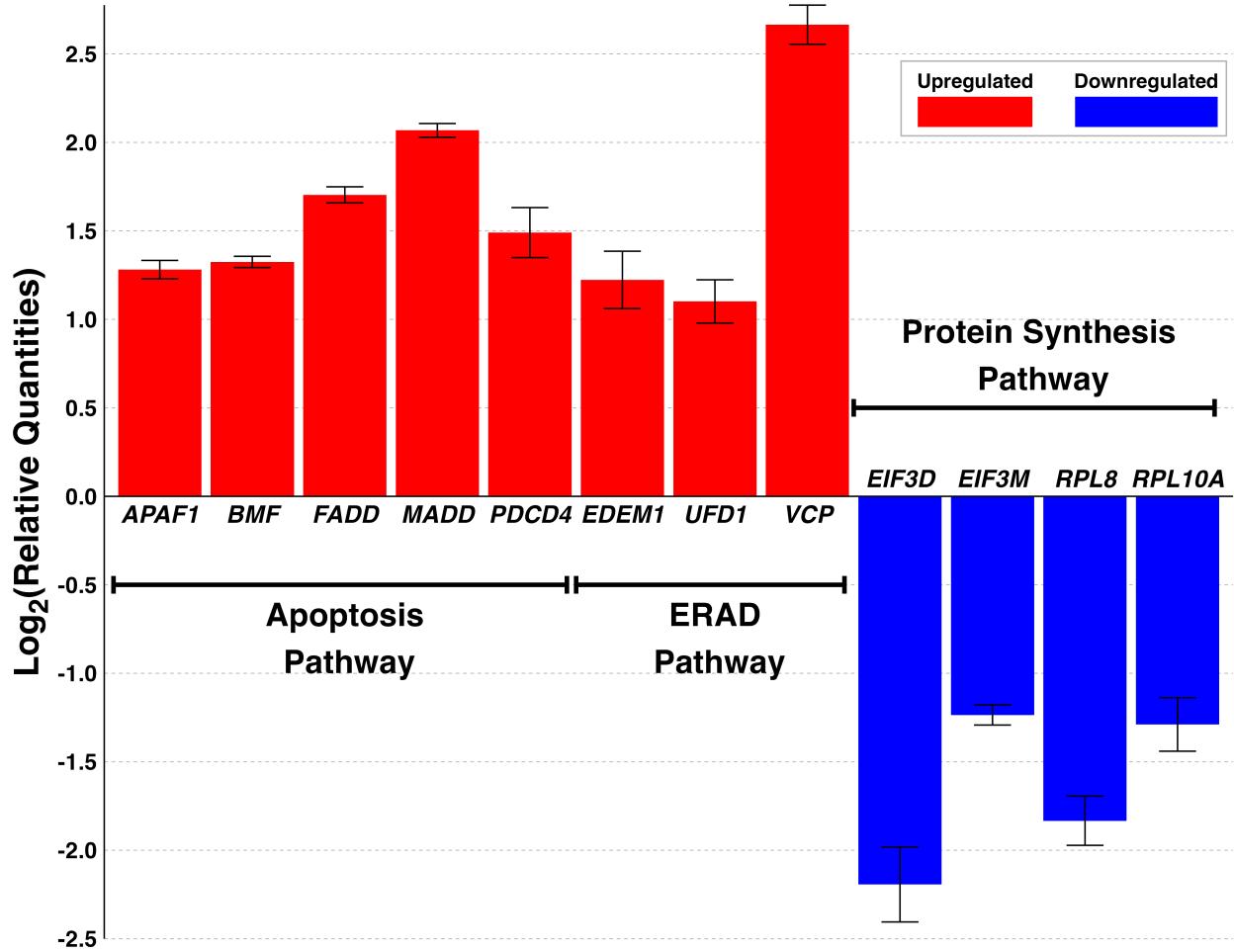


**Figure 3: DEGs of THEV-infected versus mock-infected samples at different time points. (A) Bar plot of number DEGs identified.** Red represents upregulated genes and blue represents downregulated genes. **(B) Heatmaps of scaled expression data (Z-scores) of DEGs.** DEGs identified at 12-hpi are shown 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.

## RT-qPCR Validation of Select DEGs



**Figure 5: Validation of representative DEGs involved in Apoptosis, Protein synthesis, and ER-stress responses by RT-qPCR.** MDTC-RP19 cells infected with THEV or mock infected were subjected to RT-qPCR analysis for the relative expression of the indicated DEGs at 24hpi. GAPDH was used as the internal control. Data are expressed as the mean  $\pm$  SD. All genes are statistically differentially expressed based on Student's t-test and Mann-Whitney U test.

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

Sample	Raw Reads <sup>M</sup>	Trimmed Reads <sup>M</sup>	Mapped Reads <sup>M</sup>	Uniquely Mapped Reads <sup>M</sup>	Non-uniquely Mapped Reads <sup>M</sup>	Q20%	Q30%	GC Content (%)
I_12hrsS1 <sup>Inf</sup>	40.6	39.0	34.7 (88.92%)	33.1 (84.78%)	1.6 (4.14%)	99.95	97.23	47.5
I_12hrsS3 <sup>Inf</sup>	38.8	37.3	33.1 (88.78%)	31.7 (84.95%)	1.4 (3.83%)	99.95	97.53	47.5
I_24hrsS1 <sup>Inf</sup>	42.7	41.0	36.2 (88.13%)	34.5 (84.2%)	1.6 (3.93%)	99.95	96.95	46.5
I_24hrsS2 <sup>Inf</sup>	42.0	40.4	35.6 (88.1%)	33.9 (83.83%)	1.7 (4.27%)	99.94	97.05	46.5
I_24hrsS3 <sup>Inf</sup>	40.5	38.9	34.2 (88.01%)	32.7 (84.12%)	1.5 (3.89%)	99.95	97.08	47.0
I_4hrsS1 <sup>Inf</sup>	39.1	37.4	33 (88.16%)	31.2 (83.43%)	1.8 (4.73%)	99.93	97.04	48.5
I_4hrsS2 <sup>Inf</sup>	41.3	39.6	35.3 (89.24%)	33.6 (84.92%)	1.7 (4.33%)	99.95	97.15	47.0
I_4hrsS3 <sup>Inf</sup>	41.5	39.8	35.5 (89.2%)	33.2 (83.29%)	2.4 (5.91%)	99.95	97.11	47.5
I_72hrsS1 <sup>Inf</sup>	41.2	39.8	28.3 (71.09%)	26.9 (67.7%)	1.3 (3.38%)	99.96	97.23	44.5
I_72hrsS2 <sup>Inf</sup>	39.3	38.0	27 (71.11%)	25.8 (67.86%)	1.2 (3.25%)	99.96	97.34	44.5
I_72hrsS3 <sup>Inf</sup>	39.9	37.1	28.3 (76.36%)	26.1 (70.3%)	2.2 (6.05%)	99.87	96.14	52.5
U_12hrsN1 <sup>Mk</sup>	42.1	40.4	35.9 (88.72%)	34.1 (84.39%)	1.7 (4.33%)	99.95	97.04	47.5
U_12hrsN2 <sup>Mk</sup>	41.0	39.3	34.7 (88.4%)	33.2 (84.53%)	1.5 (3.86%)	99.94	97.08	47.5
U_24hrsN1 <sup>Mk</sup>	38.4	37.0	32.7 (88.46%)	31.4 (84.74%)	1.4 (3.72%)	99.96	97.48	47.5
U_24hrsN2 <sup>Mk</sup>	39.9	38.4	34 (88.58%)	32.6 (84.96%)	1.4 (3.61%)	99.95	96.95	47.0
U_4hrsN1 <sup>Mk</sup>	39.4	37.9	33.7 (88.9%)	32 (84.41%)	1.7 (4.49%)	99.96	97.36	47.0
U_4hrsN2 <sup>Mk</sup>	37.6	34.7	22 (63.43%)	18.5 (53.18%)	3.6 (10.25%)	99.80	94.96	61.0
U_72hrsN1 <sup>Mk</sup>	50.3	47.9	15.5 (32.4%)	11.7 (24.5%)	3.8 (7.9%)	99.88	96.54	56.0
U_72hrsN2 <sup>Mk</sup>	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 <sup>M</sup>	Trimmed Reads <sup>M</sup>	Mapped Reads <sup>M</sup>	Uniquely Mapped Reads <sup>M</sup>	Non-uniquely Mapped Reads <sup>M</sup>	Q20%	Q30%	GC Content (%)
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<sup>M</sup>All values for number of reads are in millions; <sup>Inf</sup>These are infected samples indicated by the letter 'I' and 'S' in sample names; <sup>Mk</sup>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)
<b>Biological Process</b>				
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:BP	secondary alcohol biosynthetic process	7.67	13	1.58e-05

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	organonitrogen compound metabolic process	1.29	260	3.93e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	negative regulation of gene expression	2.16	40	8.52e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	negative regulation of macromolecule biosynthetic process	1.70	65	2.25e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	regulation of RNA metabolic process	1.34	154	5.97e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	intracellular transport	1.51	79	1.02e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	extrinsic apoptotic signaling pathway	4.18	10	1.89e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	transport	1.24	183	3.18e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	cell cycle phase transition	3.29	11	4.63e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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
<b>Cellular Component</b>				
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:CC	organelle lumen	1.51	135	4.91e-05

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:CC	endosome membrane	2.02	25	3.21e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
GO:CC	early endosome	2.11	22	3.70e-02
<b>Molecular Function</b>				
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:MF	transferase activity	1.30	176	1.05e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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)
<b>Biological Process</b>				
GO:BP	gene expression	3.07	289	4.61e-70

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	RNA biosynthetic process	2.55	135	4.64e-22

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	maturation of LSU-rRNA	8.13	16	1.88e-08

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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	maturity 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	maturity 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:BP	purine ribonucleoside triphosphate metabolic process	3.88	21	2.09e-05

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	regulation of cell cycle	1.95	55	1.68e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	nucleoside phosphate metabolic process	2.00	46	4.85e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	ribose phosphate biosynthetic process	2.55	24	2.07e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	'de novo' XMP biosynthetic process	18.29	4	1.71e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	negative regulation of cell cycle process	2.26	21	2.46e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	purine ribonucleoside monophosphate biosynthetic process	4.57	8	3.13e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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
<b>Cellular Component</b>				
GO:CC	ribonucleoprotein complex	5.28	181	7.13e-79
GO:CC	ribosome	8.45	100	9.07e-64

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:CC	small ribosomal subunit	10.00	37	3.59e-26

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:CC	catalytic complex	1.63	136	2.38e-07

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:CC	catalytic step 2 spliceosome	3.40	14	2.49e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:CC	prespliceosome	6.31	6	1.77e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:MF	organic cyclic compound binding	1.43	438	2.05e-17

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:MF	pyrophosphatase activity	1.65	70	2.23e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:MF	nucleotide binding	1.24	173	3.69e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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)
<b>Biological Process</b>				
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:BP	sterol biosynthetic process	6.99	17	1.44e-07

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	peptidyl-amino acid modification	2.40	42	4.49e-05

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	regulation of intracellular signal transduction	1.60	99	3.58e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	ubiquitin-dependent protein catabolic process	1.89	49	1.89e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	regulation of macromolecule metabolic process	1.22	291	3.83e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	endocytosis	1.83	41	1.20e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	embryonic morphogenesis	2.03	28	2.34e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	protein ubiquitination	1.60	51	3.47e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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
<b>Cellular Component</b>				
GO:CC	cytoplasm	1.30	827	6.20e-27

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:CC	endoplasmic reticulum membrane	1.98	84	1.17e-07

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:CC	cation-transporting ATPase complex	4.14	11	4.36e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:MF	misfolded protein binding	7.40	10	9.76e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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)
<b>Biological Process</b>				
GO:BP	translation	5.77	136	3.59e-65
GO:BP	gene expression	2.26	288	1.04e-39
GO:BP	metabolic process	1.43	761	3.14e-36

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	protein-RNA complex organization	4.20	41	8.95e-13

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	amino acid metabolic process	2.61	52	4.48e-08

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	cellular component organization or biogenesis	1.25	417	3.54e-06

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	ribose phosphate metabolic process	2.16	48	4.64e-05

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	ATP biosynthetic process	5.95	11	2.49e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	proteinogenic amino acid metabolic process	2.46	26	1.73e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	deoxyribonucleotide biosynthetic process	6.37	8	3.90e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	microtubule-based process	1.44	85	1.63e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	purine nucleoside diphosphate catabolic process	3.46	11	2.38e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	mitotic DNA integrity checkpoint signaling	3.06	12	3.38e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:BP	regulation of double-strand break repair	2.90	12	4.90e-02

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
<b>Cellular Component</b>				
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:CC	large ribosomal subunit	6.31	51	3.76e-26

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:CC	nuclear protein-containing complex	1.60	136	7.62e-07

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:CC	protein-DNA complex	1.72	65	3.03e-04

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:CC	pICln-Sm protein complex	9.89	5	8.41e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:MF	rRNA binding	6.56	24	3.02e-11

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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:MF	catalytic activity	1.13	553	9.04e-03

GO Category	GO:Term	Fold Enrichment	Number of DEGs	P-value (Adjusted)
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
12-hpi	down	Nucleocytoplasmic transport	22	2.29	1.00e-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	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
24-hpi	down	Propanoate metabolism	12	3.24	7.53e-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	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
12-hpi	down	Base excision repair	9	1.15e-03

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	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

415 **SUPPLEMENTARY INFORMATION/MATERIALS**

Table S3: Primers for RT-qPCR Validation of RNA-seq data

Entrez ID	Target Gene	Forward Primer	Reverse Primer	Amplicon Size
100549497	<i>APAF1</i>	GCTGCGCAAATACCCGAGGTC <sup>ExJ</sup>	GCCAGACACAGCATACTGTCACAC <sup>ExJ</sup>	133 bp
100550591	<i>BMF</i>	CGGAGACTCTTCTATGGGAATGCTGG <sup>ExJ</sup>	CTGCTGATGCCGCTGTATGTGG <sup>ExJ</sup>	189 bp
100543065	<i>EDEM1</i>	CTGGACTACAGGTGTTGATAGGAGACG <sup>ExJ</sup>	CCACTAACTCTGGCCTCAGTGG	159 bp
100545922	<i>EIF3D</i>	GCACAGAGGAACCTTCGGAGAG <sup>ExJ</sup>	GTCACGAGGCTTCTGCTGTGAC <sup>ExJ</sup>	180 bp
100545633	<i>EIF3M</i>	CTCTCAGACTGCAGCTACTGAGC <sup>ExJ</sup>	GTCTGTGCTGAGGTTCCAGTCAG	179 bp
100540536	<i>FADD</i>	GGAGCTCTGCAACTTCCTCATGG	CCTTCATGTCAGGCCACTCATCAG	167 bp
100303685	<i>GAPDH<sup>HK</sup></i>	CACTATCTTCCAGGAGCGTGACC <sup>ExJ</sup>	CTGAGATGATAACACGCTTAGCACAC	146 bp
100551463	<i>MADD</i>	GAGCTGACGAGGTTGAACTTGCTG <sup>ExJ</sup>	CTGGCTCCAATGATAACAAGGTAGTCG	200 bp
100547583	<i>PDCD4</i>	GCACAGTAGAAGTGGAGAACATCTGAGTG <sup>ExJ</sup>	CTTCCTCAACCGCCTTTGC	161 bp
100544053	<i>RPL10A</i>	GGCACCGTCAGGCTGAAGTC <sup>ExJ</sup>	GGCATCGTACTTCTTAGCCAGCTC <sup>ExJ</sup>	177 bp
100544011	<i>RPL8</i>	GCCGAGAGACATGGCTACATCAAGG	CAGCTGAGCTTCTGCCACAG <sup>ExJ</sup>	186 bp
104913522	<i>UFD1</i>	GTGGTCTGCTTCAACATCTGGTC <sup>ExJ</sup>	GATCTATGAGCTTCGGTAATGGAGAC <sup>ExJ</sup>	154 bp
100548376	<i>VCP</i>	CAAGGCCATAGGAGTGAAGCCTC <sup>ExJ</sup>	CTCAGGTTGCTCTCAGACTCACC	171 bp

<sup>HK</sup> Control (house-keeping) gene<sup>ExJ</sup> Primer spans exon-exon junction;