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Supplemental information

Multi-OMICs landscape of SARS-CoV-2-induced host responses in human lung epithelial cells

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Supplementary Data

Supplementary Tables

Table S1 related to Figure 1 and Figure 2.

List of differentially regulated transcripts identified in Calu-3 cells infected with SARS-CoV-2/ Trondheim-S15/2020 strain at time intervals 3-, 6-, 12-, 24-, and 48-hours post-infection (hpi).

Table S2 related to Figure 1 and Figure 2. List of differentially expressed proteins identified in Calu-3 cells infected with SARS-CoV-2/ Trondheim-S15/2020 strain at time intervals 3-, 6-, 12-, 24-, and 48-hours post-infection (hpi).

Table S3 related to Figure 1 and Figure 3. List of differentially phosphorylated proteins and phosphosites identified in Calu-3 cells infected with SARS-CoV-2/ Trondheim-S15/2020 strain at time intervals 3-, 6-, 12-, 24-, and 48-hours post-infection (hpi).

Table S4 related to Figure 1 and Figure 3. List of differentially acetylated proteins and acetylation sites identified in Calu-3 cells infected with SARS-CoV-2/ Trondheim-S15/2020 strain at time intervals 3-, 6-, 12-, 24-, and 48-hours post-infection (hpi).

Table S5 related to Figure 3. Pathways enriched in the 8 phosphoproteome clusters

Table S6 related to Figure 1 and Figure 4. Exometabolomics data from Calu-3 cells infected with SARS-CoV-2 at time intervals 3-, 6-, 12-, 24-, and 48-hours post-infection (hpi).

Table S7 related to Figure 5. Viral omics profile from Calu-3 cells infected with SARS-CoV-2 at time intervals 3-, 6-, 12-, 24-, and 48-hours post-infection (hpi).

Supplementary Figures

Supplementary Figure S1 related to Figure 1. Correlation graphs comparing **A.** transcriptome and **B.** proteome results of uninfected Calu-3 cells across our and other studies. Correlation graphs depicting replicate samples and various time points for SARS-CoV-2/ Trondheim-S15/2020 strain infected Calu-3 cell **C.** transcriptome **D.** total proteome, **E.** phosphoproteome, and **F.** acetylome data.

Supplementary Figure S2 related to Figure 2. **A.** Biological Processes (GO-BP) enriched in the Calu-3 transcriptome and proteome after SARS-CoV-2 infection. **B.** An Upset graph showing overlap of differentially expressed proteins in lung cell lines in response to SARS-CoV-2 infection between the current study and various published datasets, including Thorn *et al.*, Hekman *et al.*, Grossegeisse *et al.*, and Stukalov *et al.* **C.** Heatmap depicting transcript levels of cytokines and chemokines in Calu-3 cells at time intervals 3, 6-, 12-, 24-, and 48-hours post-infection (hpi). **D.** A scan of the cytokine array showing changes in levels of cytokines in Calu-3 cells infected with SARS-CoV-2/ Trondheim-S15/2020 strain at time intervals 3, 6-, 12-, 24-, and 48-hours post-infection (hpi).

Supplementary Figure S3 related to Figure 3. **A.** An Upset graph showing overlap of hyperphosphorylated proteins in lung cell lines in response to SARS-CoV-2 infection between the current study and various published datasets, including Thorn *et al.*, Hekman *et al.*, and Stukalov *et al.* **B.** Heatmap showing enriched upstream kinases from the phosphoproteomics profile of Calu-3 cells after SARS-CoV-2 infection **C.** Statistics of differentially phosphorylated transcription factors in response to SARS-CoV-2 infection **D.** Heatmap showing changes in the levels of transcription factors after SARS-CoV-2 infection. **E.** Graph showing changes in Lysine (K) acetylation sites, Serine (S) phosphorylation sites and protein abundance of Vimentin (VIM). **F.** Graph showing changes in Lysine (K) acetylation and ubiquitination sites of leucine rich repeat containing 59 (LRRC59)

Supplementary Figure S4 related to Figure 4. Comparison of intracellular ^{94,95} and extracellular levels of **A, B** glycolysis metabolites, **C, D.** TCA cycle metabolites and **E, F.** amino acids

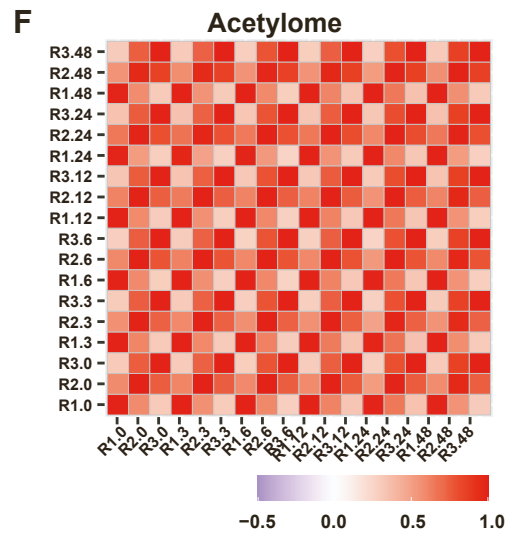
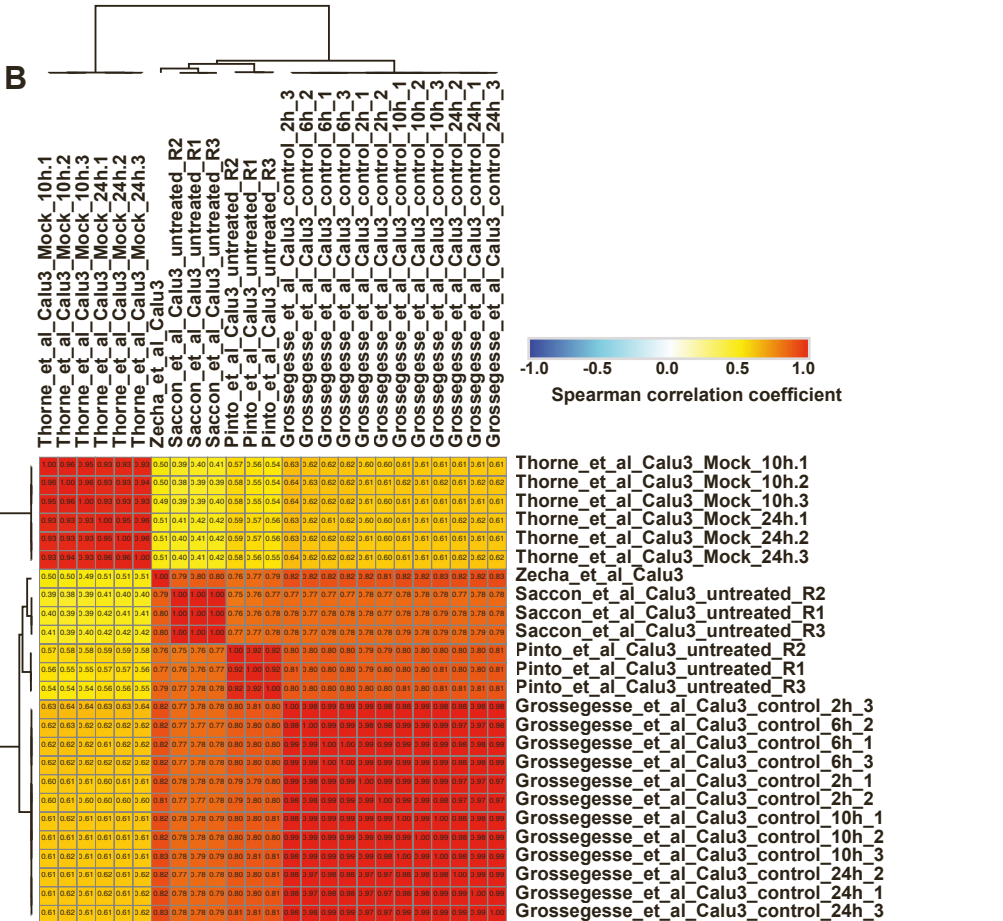
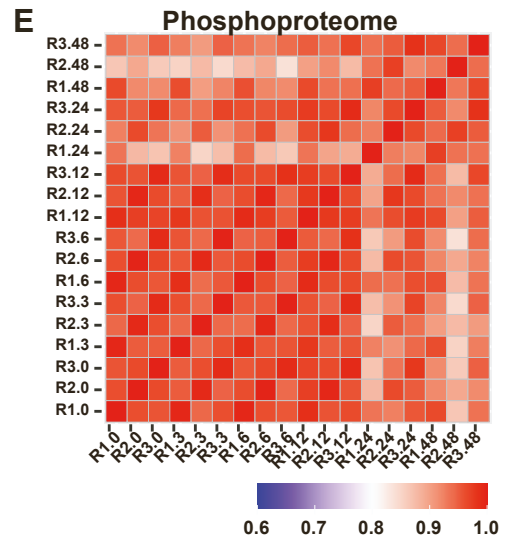
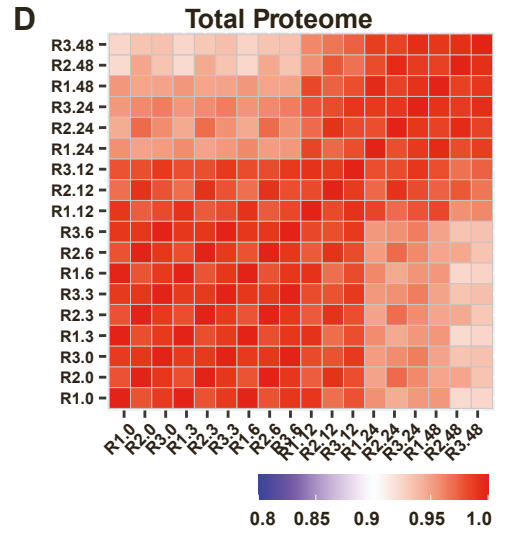
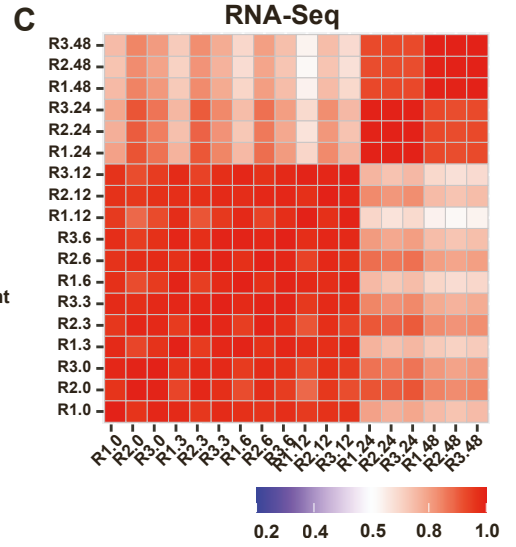
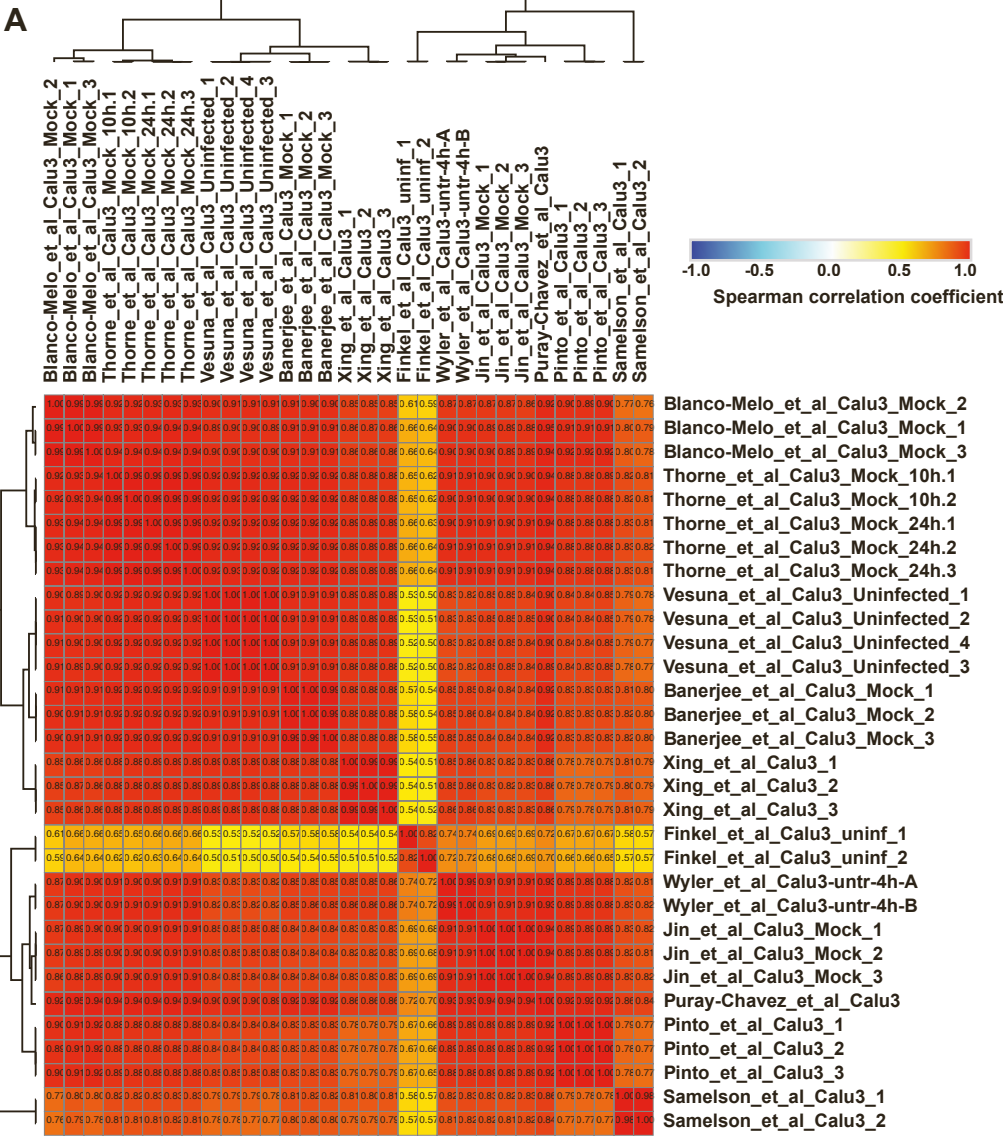
Supplementary Figure S5 related to Figure 5. Phosphorylation sites unique to this study are presented as magenta sticks, whereas common sites are in cyan. Experimental structural models of **A.** ORF7a (PDB ID 6w37), **B.** ORF8 (PDB ID 7jx6), **C.** ORF9b (PDB ID 7kdt) and Robetta models of **D.** N protein **E.** ORF3a, **F.** ORF6, **G.** Rep1a, **H.** Nsp3, and **I.** Protein M are shown in rainbow cartoon representation (N-to-C blue to red). Missing regions of Protein N and Rep1a Nsp1 were modelled with Robetta and presented as a rainbow cartoon, and were hidden where experimental structures of Protein N (PDB ID 6vyo for NTD, in olive and PDB ID 6wzo for CTD, in grey) and Rep1a Nsp1 (PDB ID 7k7p for NTD, in teal and PDB ID 7jqb for CTD, in purple) were overlapping with the models. The second protomer of ORF3a (PDB ID 7kjr in grey) and Tom70, the interaction partner of ORF9b (PDB ID 7kdt, in tan) are shown in uniform colors. Selected hydrogen bonds are shown as cyan dotted lines. The figure was prepared with ChimeraX (Goddard et al doi: 10.1002/pro.3235)

Supplementary Figure S6 related to Figure 6. Graphs showing the average trend of differentials from transcriptomics, proteomics, and phosphoproteomics datasets with respect to various pathways and processes, including **A.** Alternative splicing by spliceosome **B.** Regulation of mRNA splicing via spliceosome. Heatmaps showing differential changes of transcripts, proteins and phosphorylation sites for **C.** Hippo signaling **D.** Regulation of Hippo signaling, **E.** DNA damage response, **F.** DNA repair, **G.** Protein ubiquitination, **H.** Regulation of protein mono and polyubiquitination **I.** Graph showing protein expression levels of Ubiquitin (Ub) E2 and E3 ligases in response to SARS-CoV-2 infection. **J.** Heatmap showing changes in proteins involved in regulation of the cell cycle.

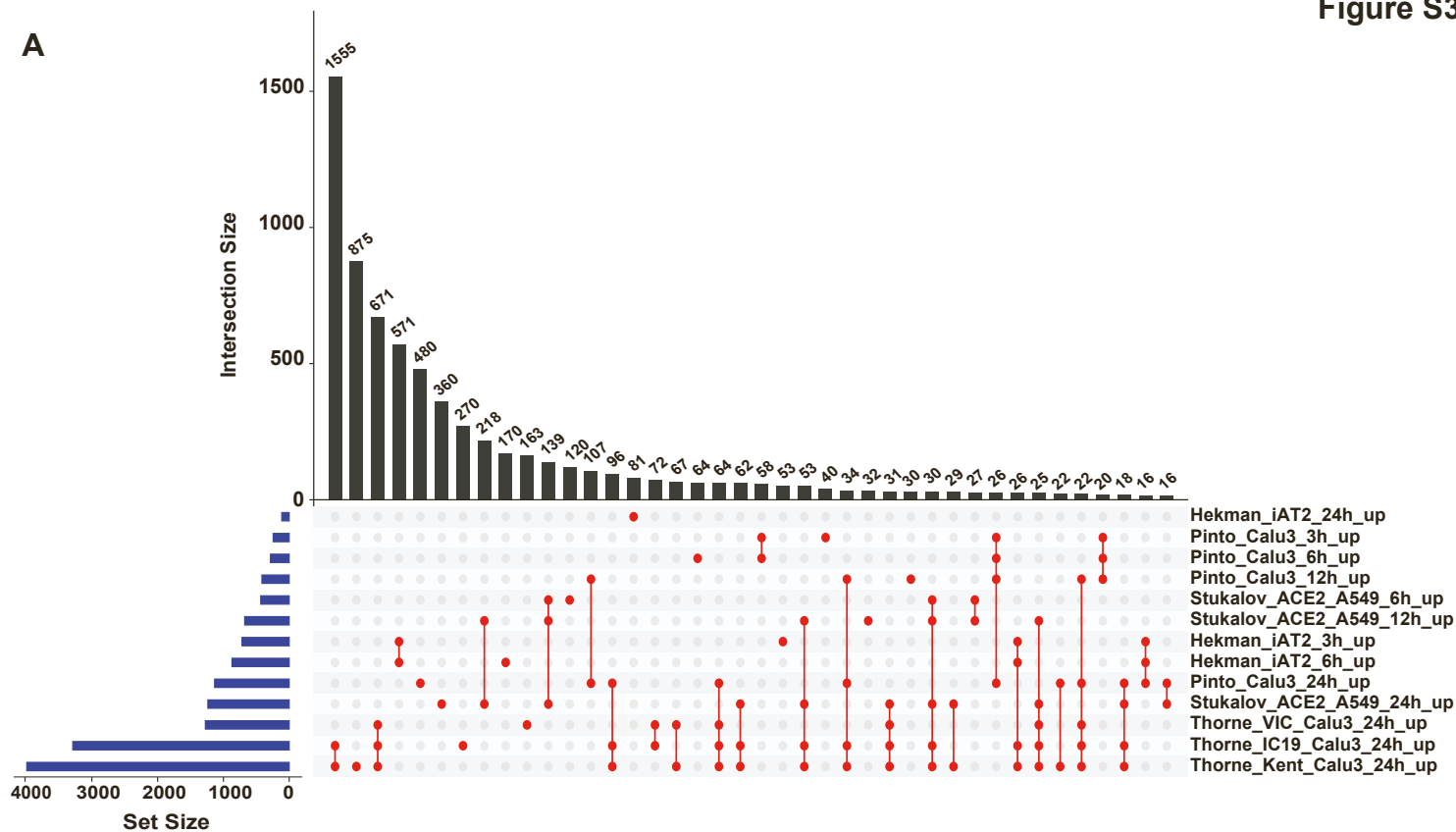
Supplementary Figure S7 related to Figure 6. Heatmaps showing **A.** transcriptome, proteome **B.** phosphoproteome, and **C.** acetylome changes in genes/proteins belonging to glycolysis, TCA cycle and amino acid metabolism pathways in response to SARS-CoV-2 infection.

Gassen, N.C., Papiès, J., Bajaj, T., Emanuel, J., Dethloff, F., Chua, R.L., Trimpert, J., Heinemann, N., Niemeyer, C., Weege, F., et al. (2021). SARS-CoV-2-mediated dysregulation of metabolism and autophagy uncovers host-targeting antivirals. *Nat Commun* *12*, 3818. [10.1038/s41467-021-24007-w](https://doi.org/10.1038/s41467-021-24007-w).

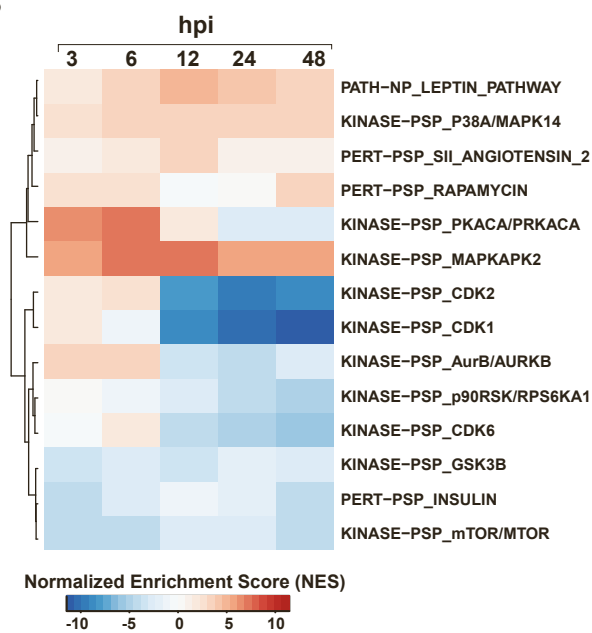
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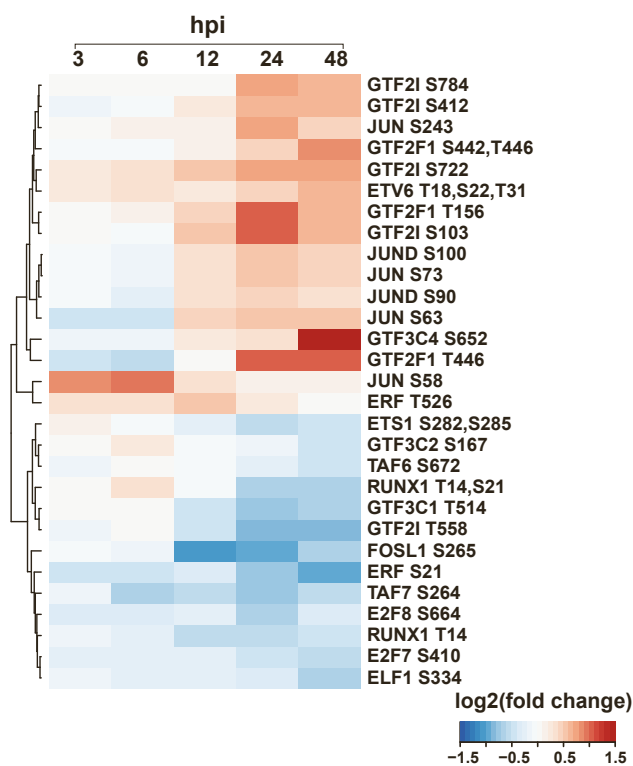
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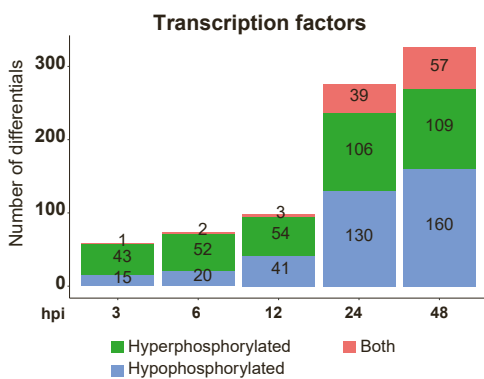
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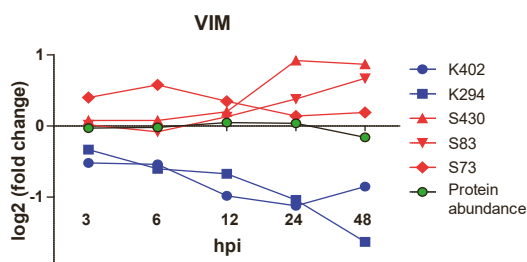
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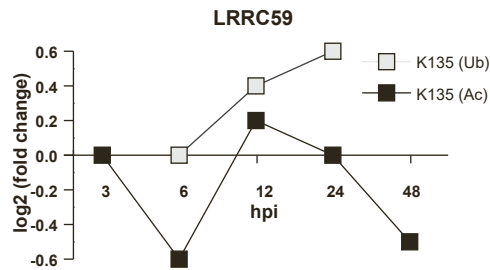
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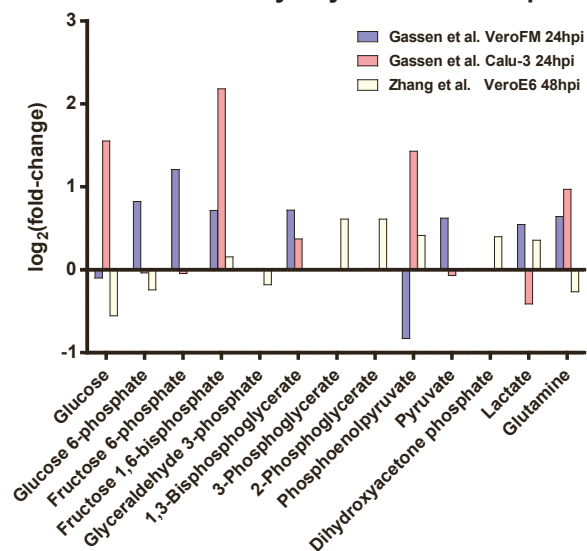
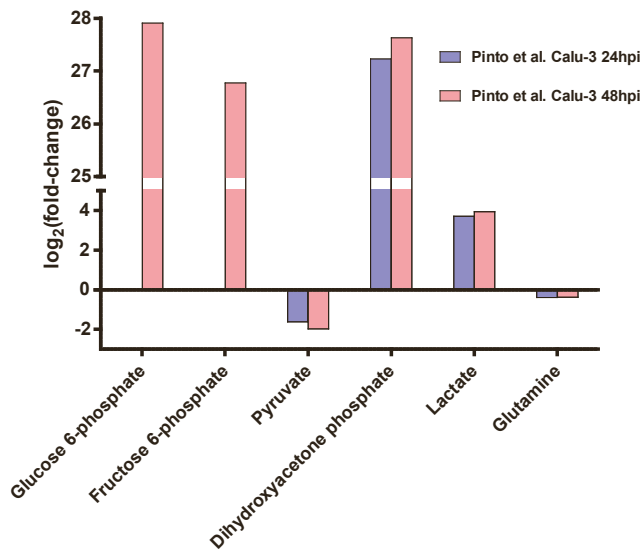
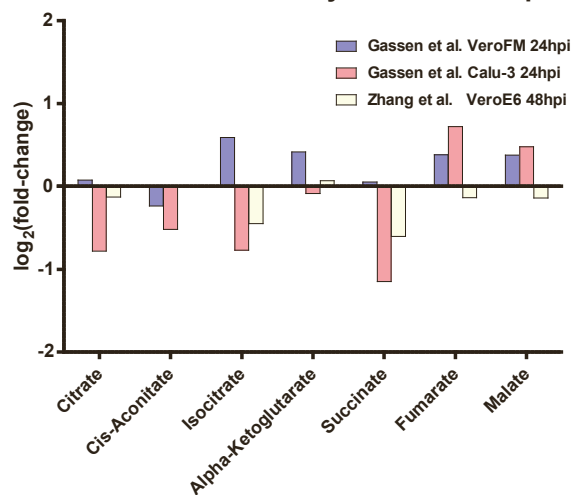
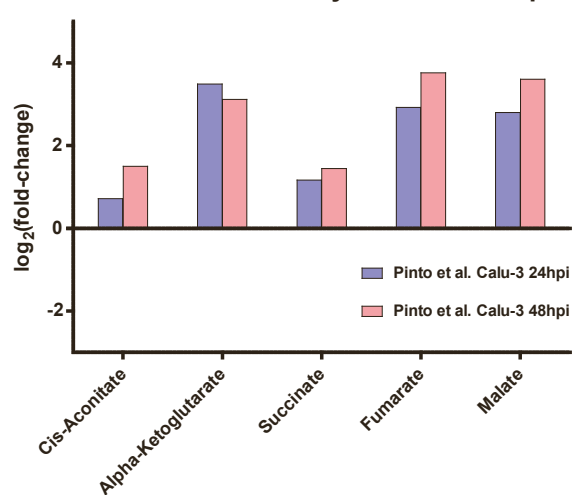
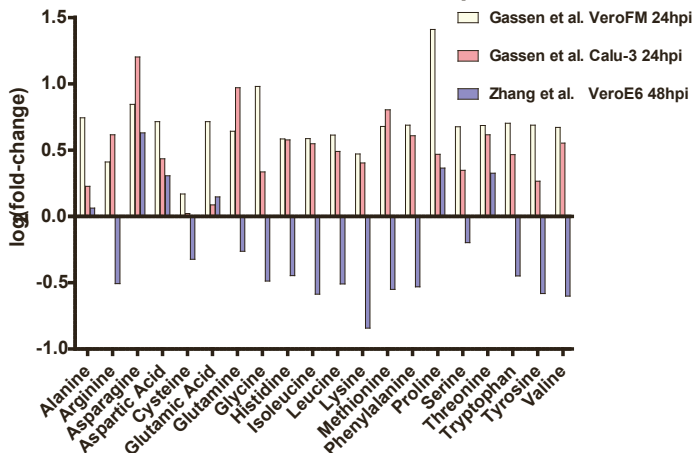
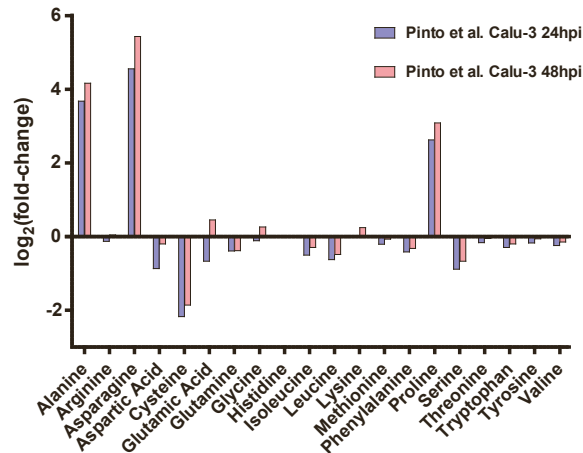


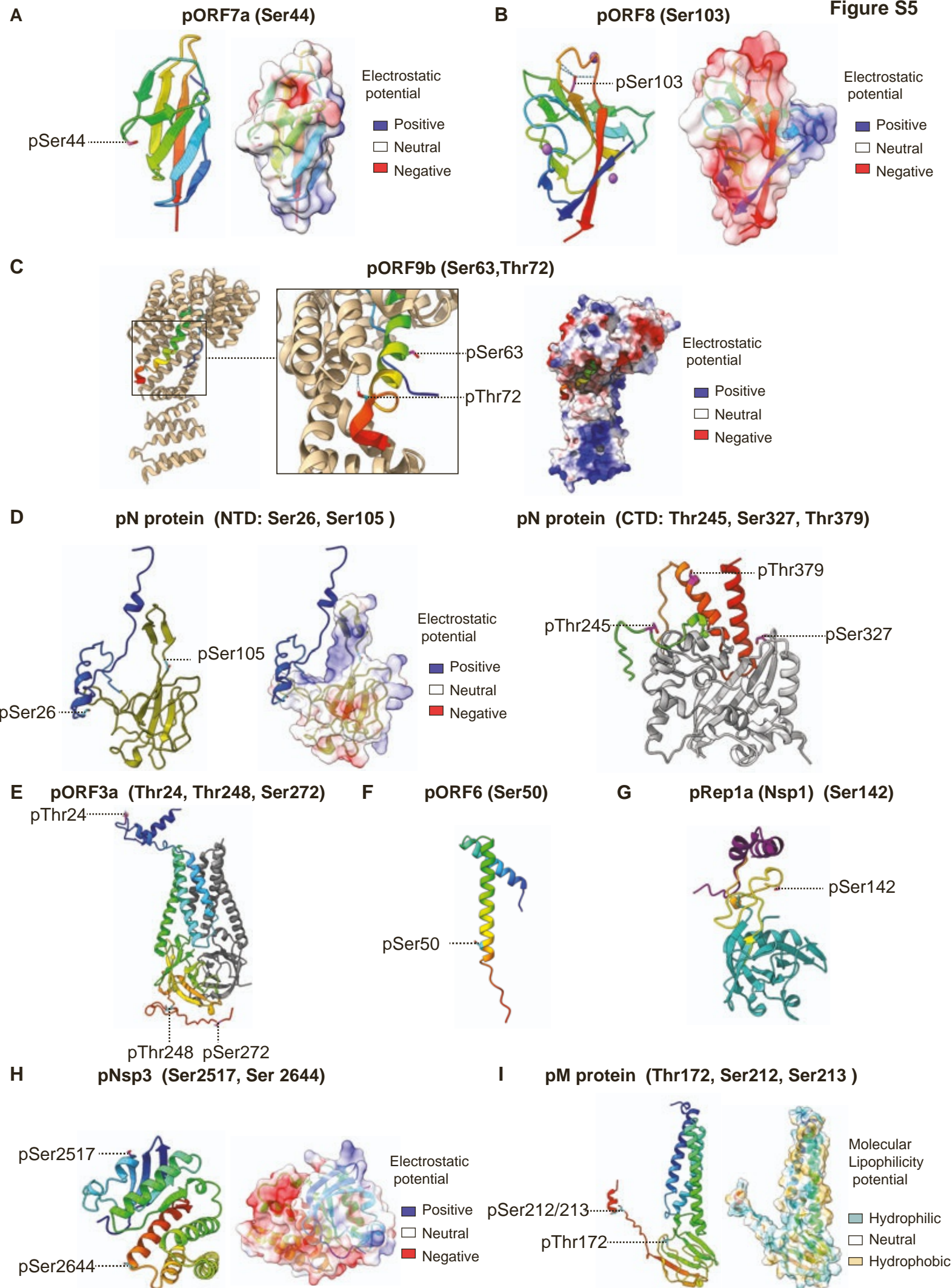
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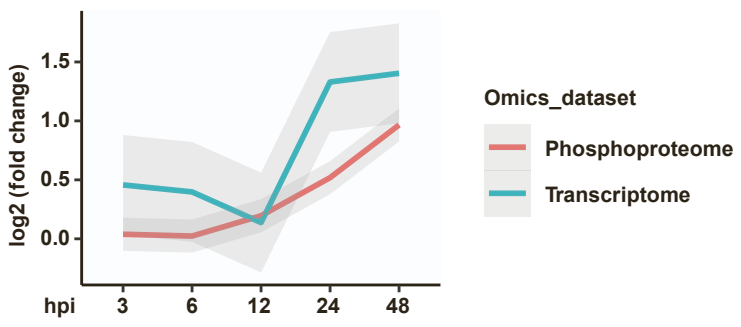
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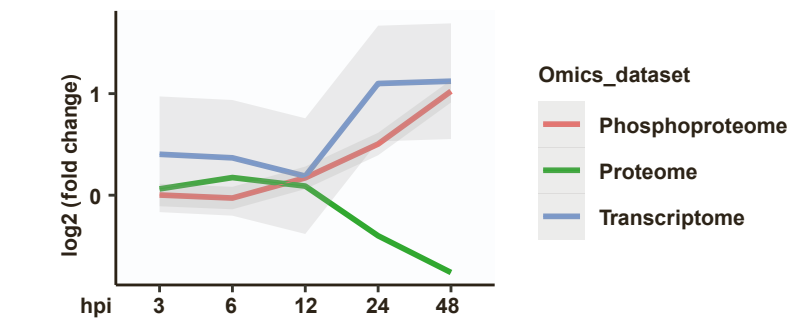
A Intracellular Glycolysis metabolite profile**B Extracellular Glycolysis metabolite profile****C Intracellular TCA cycle metabolite profile****D Extracellular TCA cycle metabolite profile****E Intracellular amino acid profile****F Extracellular amino acid profile**



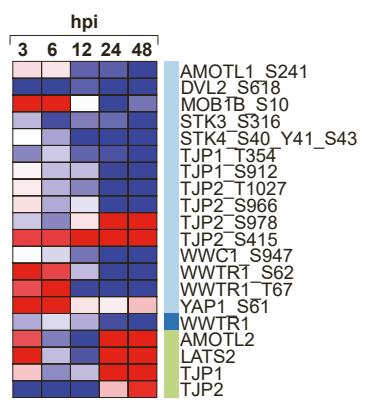
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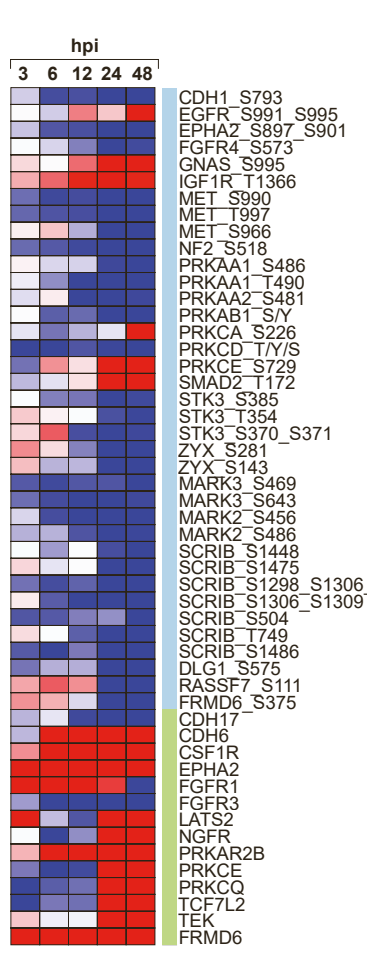
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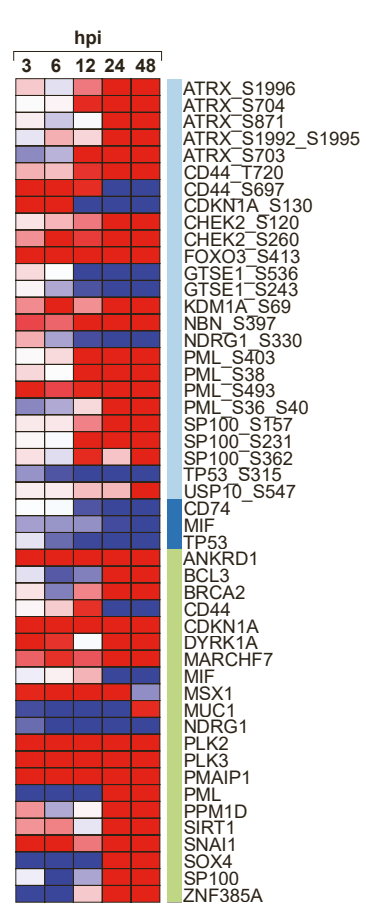
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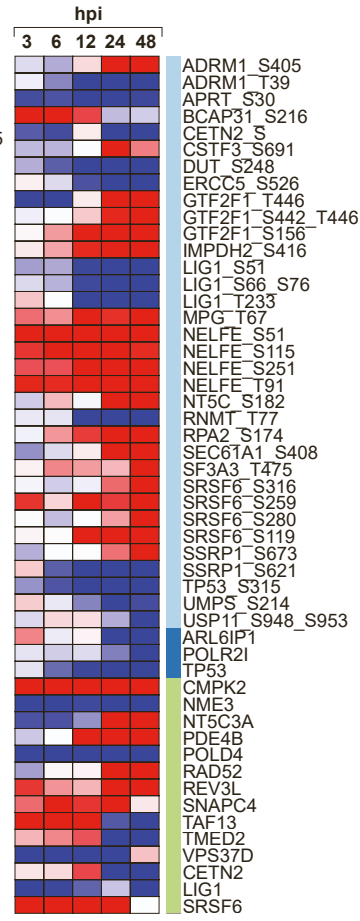
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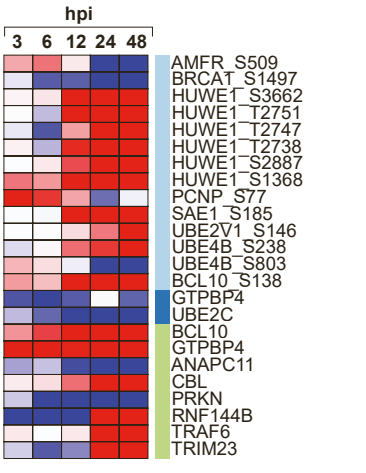
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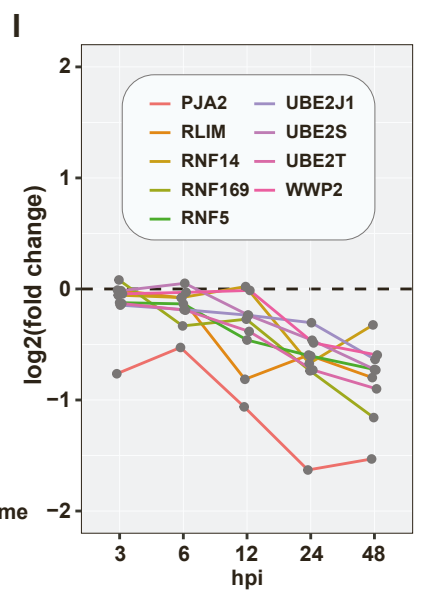
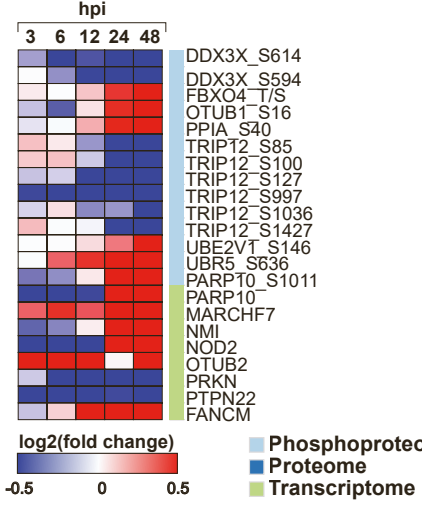
F DNA repair



G Protein Ubiquitination



H Regulation of Protein Mono and Polyubiquitination



J Regulation of cell cycle process

