

Supporting Information

Dengue virus rapidly reshapes the transcriptional landscape of human neutrophils toward cytokine storm–associated inflammation

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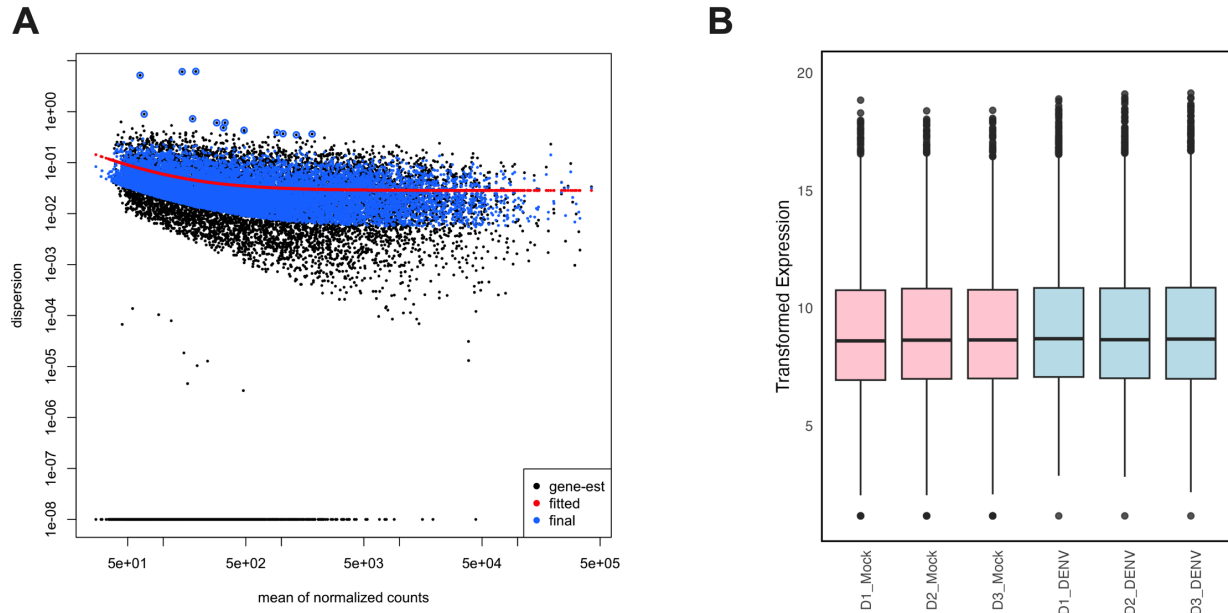
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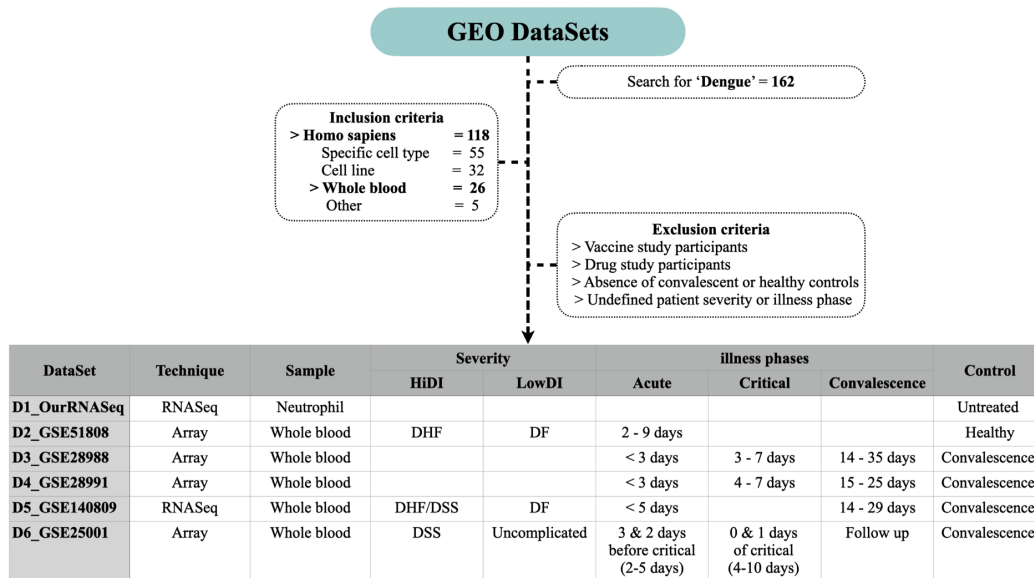
*** Correspondence:**

Supranee Phanthanawiboon

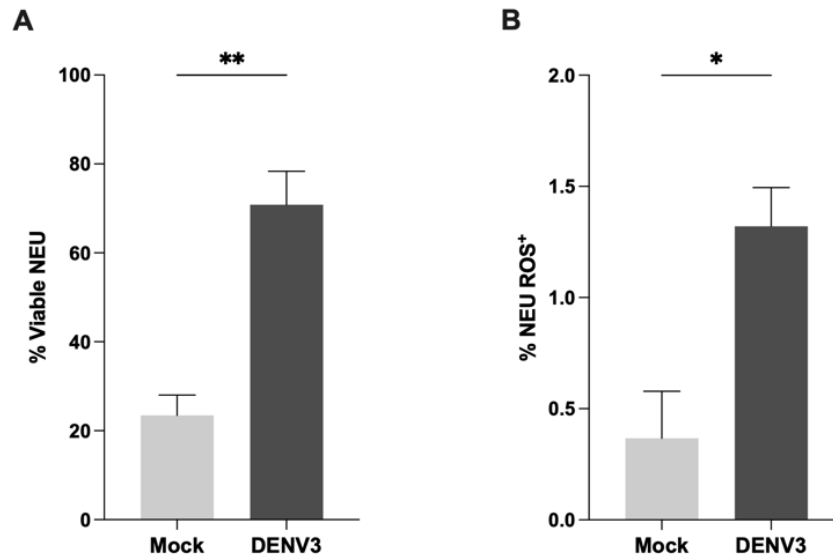
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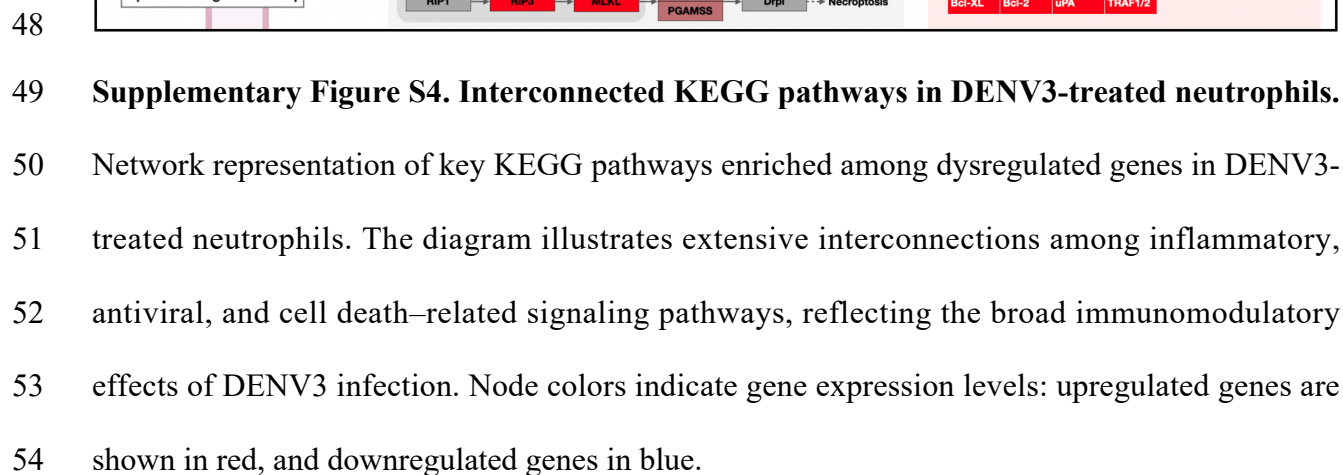
Supplementary Figure S1. Quality control and normalization of RNA-seq data using DESeq2. (A) Dispersion plot showing gene-wise dispersion versus mean normalized counts. Black dots represent raw dispersion estimates, the red line shows the fitted trend, and blue dots indicate shrunk final estimates, confirming appropriate fit to the negative binomial model. (B) Boxplot of variance-stabilized counts for Mock-infected (pink) and DENV-infected (blue; D1–D3) samples, demonstrating consistent distributions and effective normalization across conditions.



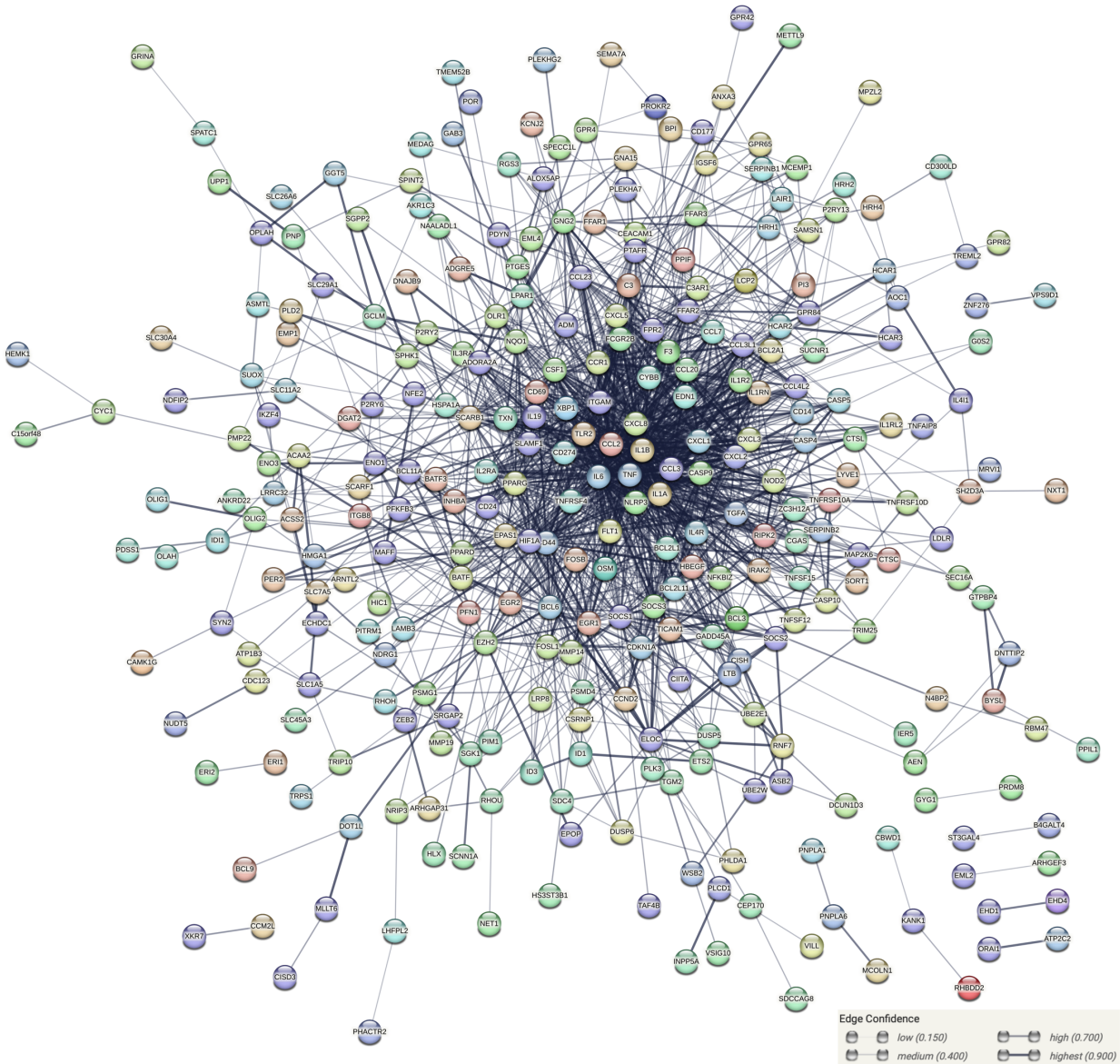
Supplementary Figure S2. Selection of GEO datasets for dengue transcriptomic meta-analysis. Flow diagram and summary table illustrating the selection of publicly available GEO datasets included in this study. Datasets were retrieved using the search term “Dengue” (n = 162) and screened based on inclusion criteria (human samples, specific cell type, PBMCs, or whole blood) and exclusion criteria (vaccine-only participants, absence of confirmed acute dengue cases, or unmatched severity/illness-phase metadata). The final selected datasets include neutrophil RNA-seq and whole-blood or PBMC microarray studies categorized by severity (DF, DHF, DSS) and illness phases (acute, critical, convalescence), with corresponding control groups.



Supplementary Figure S3. Representative flow cytometry analysis of neutrophils. Isolated neutrophils were co-cultured with medium (Mock) or DENV3 (MOI = 1) prior to assessment of cell viability and ROS production. Cumulative data for cell viability (a) and ROS production (b) are presented as the percentages of viable cells and ROS⁺ cells, respectively, at 24 hours post-incubation (p.o.i.). Data are presented as mean $\pm$ SEM. * $p < 0.05$ and ** $p < 0.01$



Network representation of key KEGG pathways enriched among dysregulated genes in DENV3-treated neutrophils. The diagram illustrates extensive interconnections among inflammatory, antiviral, and cell death-related signaling pathways, reflecting the broad immunomodulatory effects of DENV3 infection. Node colors indicate gene expression levels: upregulated genes are shown in red, and downregulated genes in blue.



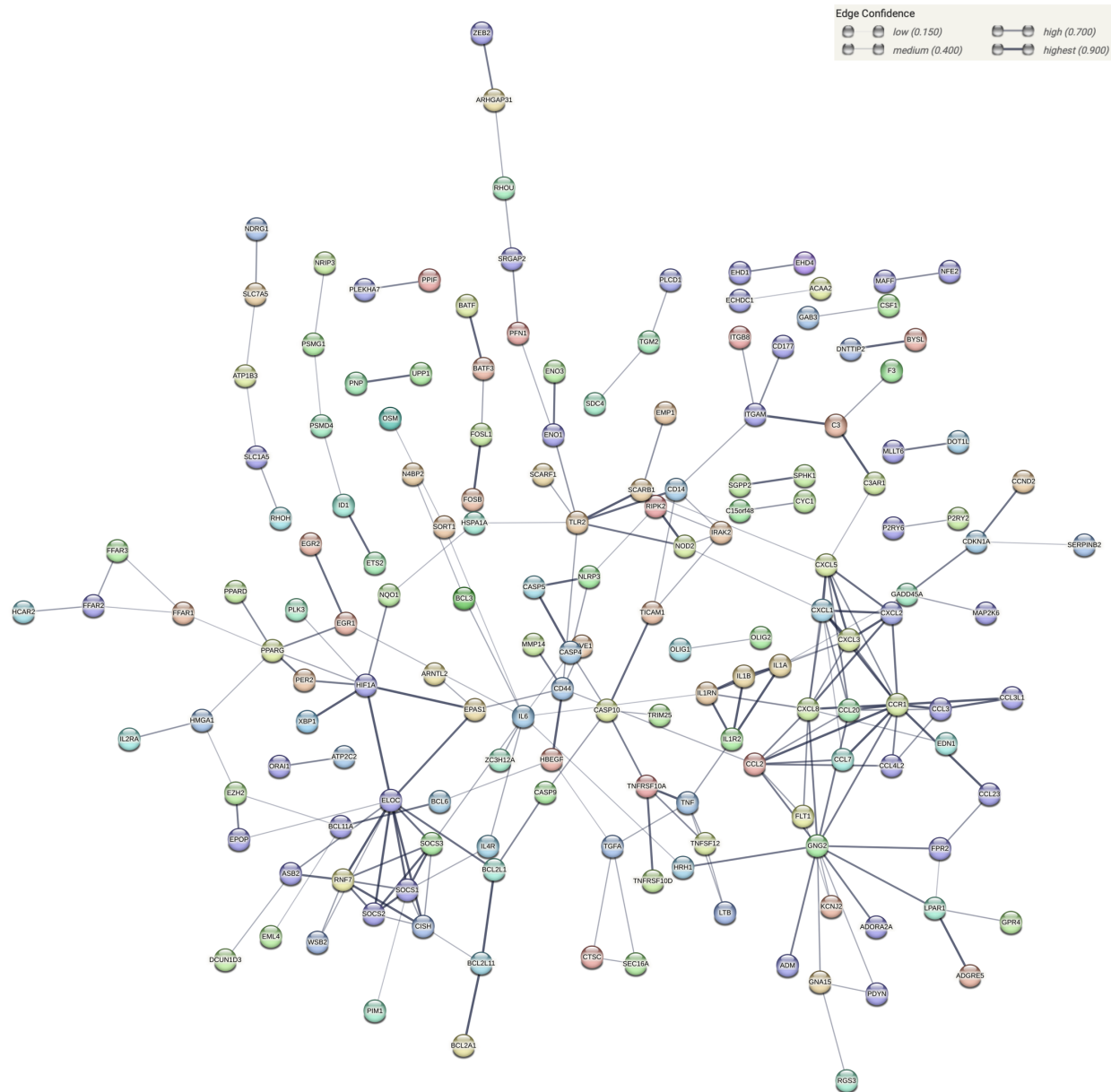
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56 **Supplementary Figure S5. Full protein–protein interaction network of DENV3-treated**

57 **neutrophils.** Diagram displaying the complete protein–protein interaction (PPI) network

58 generated from significantly upregulated genes using STRING. Each node represents a protein,

59 and edge density indicates the confidence level of the interaction.



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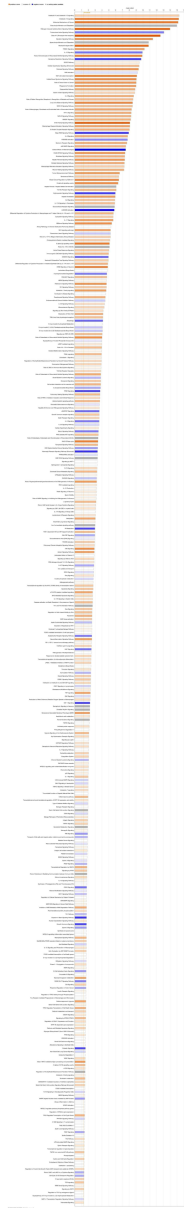
61 **Supplementary Figure S6. Physical protein–protein interaction subnetwork of DENV3-**

62 **treated neutrophils.** Diagram displaying the physical protein–protein interaction (PPI)

63 subnetwork generated from the full STRING PPI network, filtered to include only experimentally

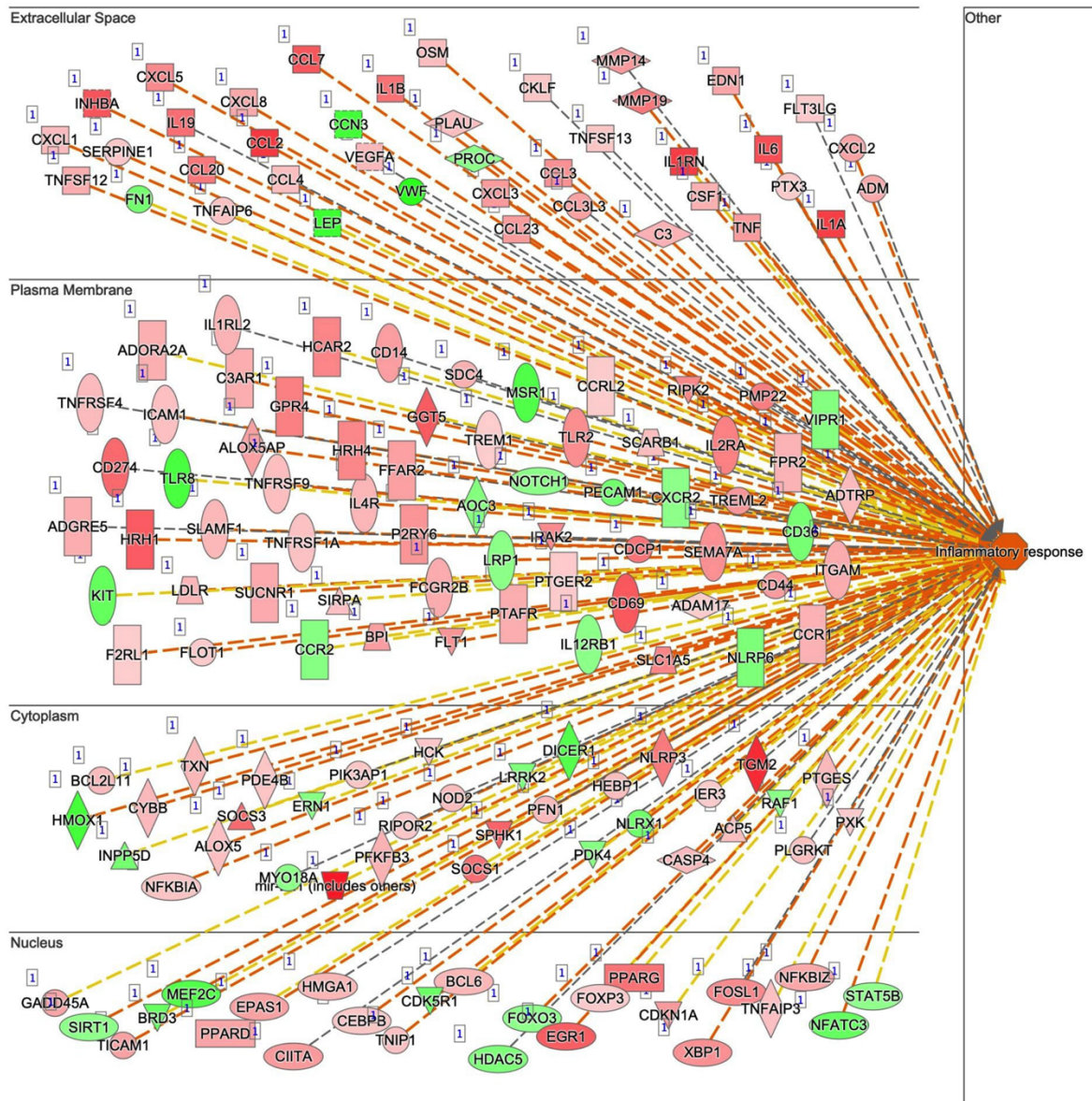
64 supported physical interactions. Each node represents a protein, and edge density indicates the

65 confidence level of the interaction.

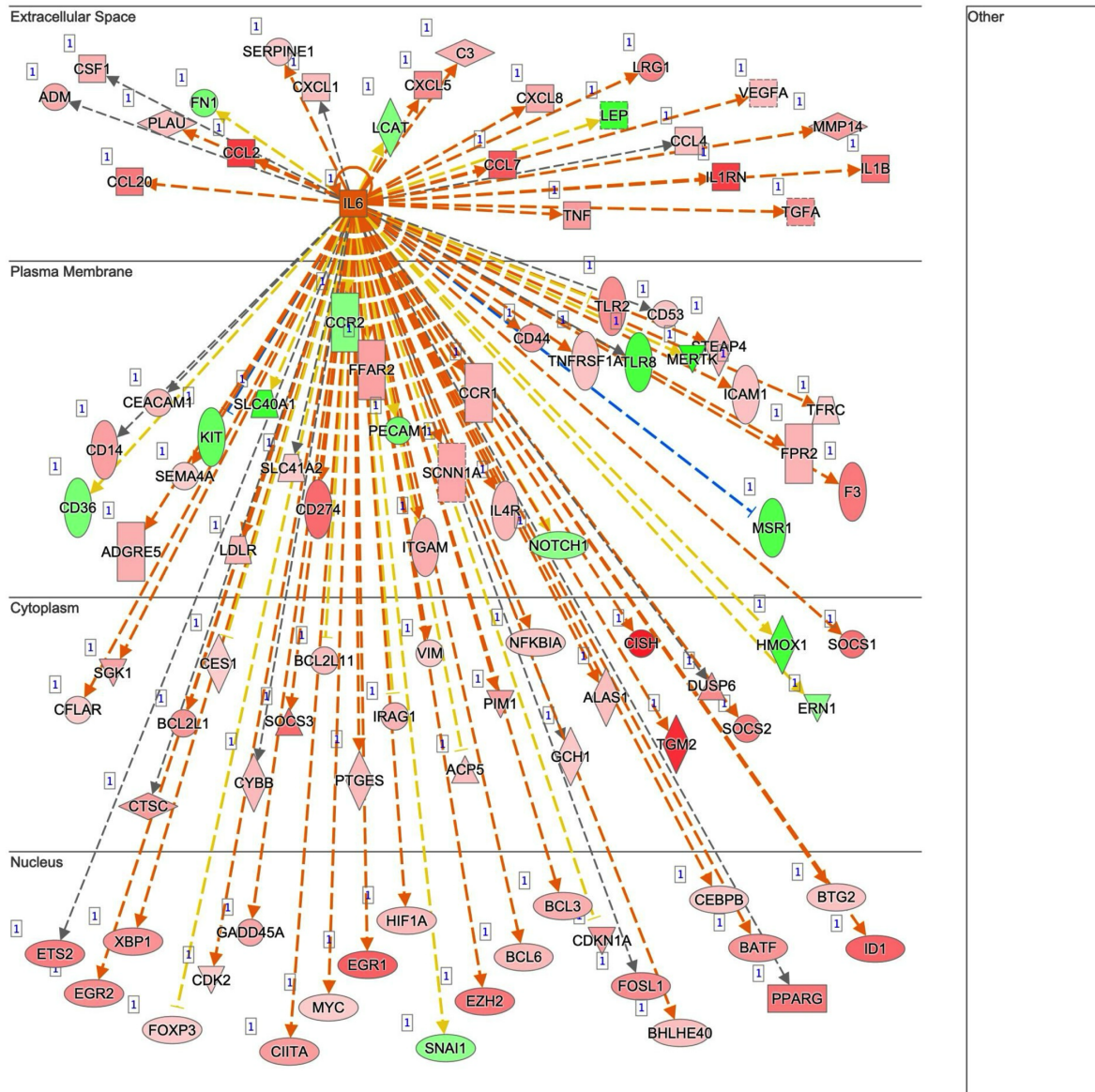


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67 **Supplementary Figure S7. Canonical pathway enrichment of DENV3-treated neutrophils**
68 **analyzed using IPA.** Ranked bar plot generated by Ingenuity Pathway Analysis (IPA) showing
69 significantly altered canonical pathways. Bars represent pathway activation Z-scores, with positive
70 values (orange) indicating predicted activation and negative values (blue) indicating predicted
71 inhibition.

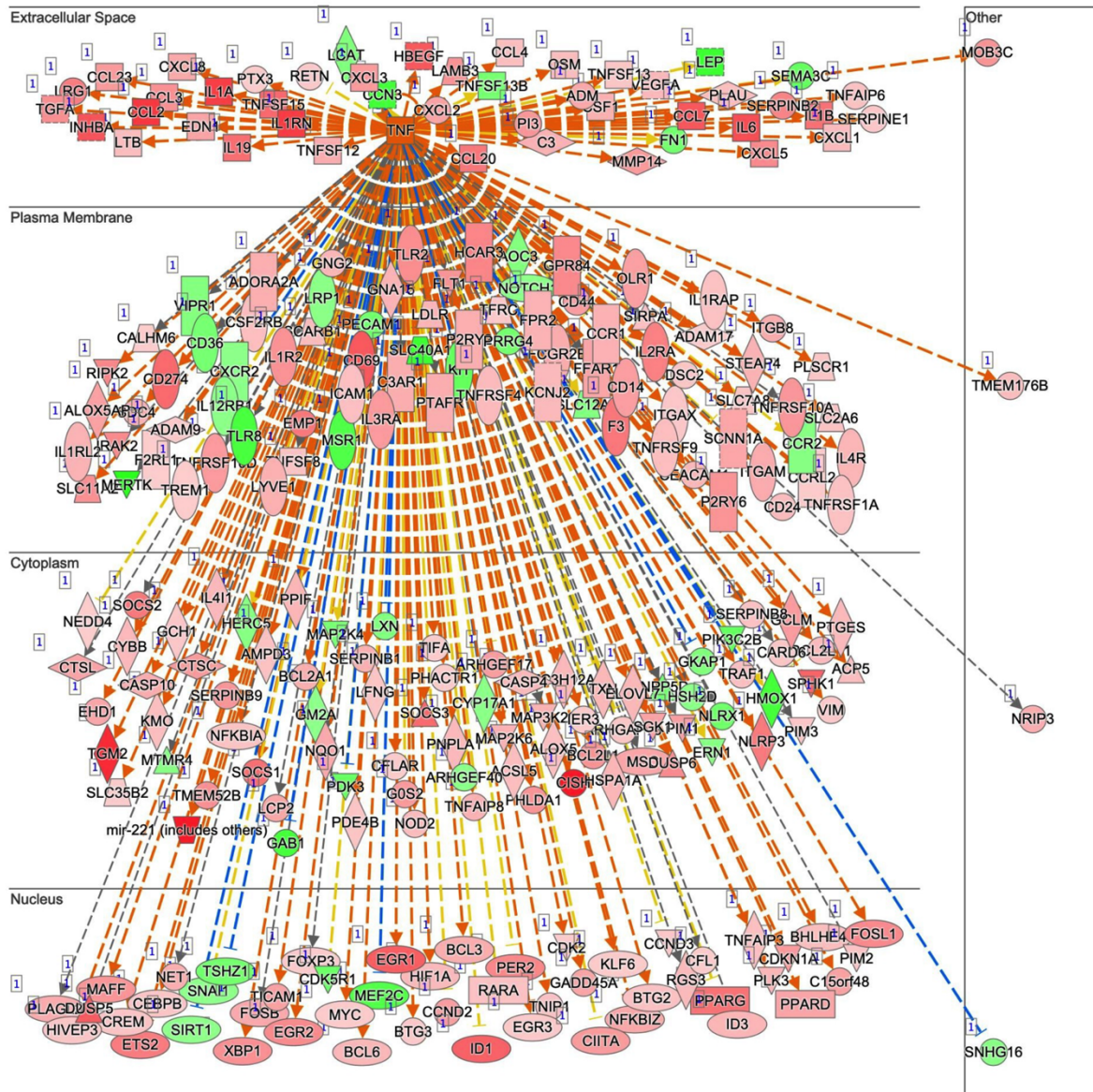


Supplementary Figure S8. IPA causal network of inflammatory response in DENV3-treated neutrophils. IPA network illustrating predicted upstream regulators, intermediates, and effector genes driving the inflammatory response. Node colours show gene expression changes (red: upregulated; green: downregulated), and edge colours indicate predicted activation or inhibition based on IPA causal inference. Cellular compartments are annotated for context.

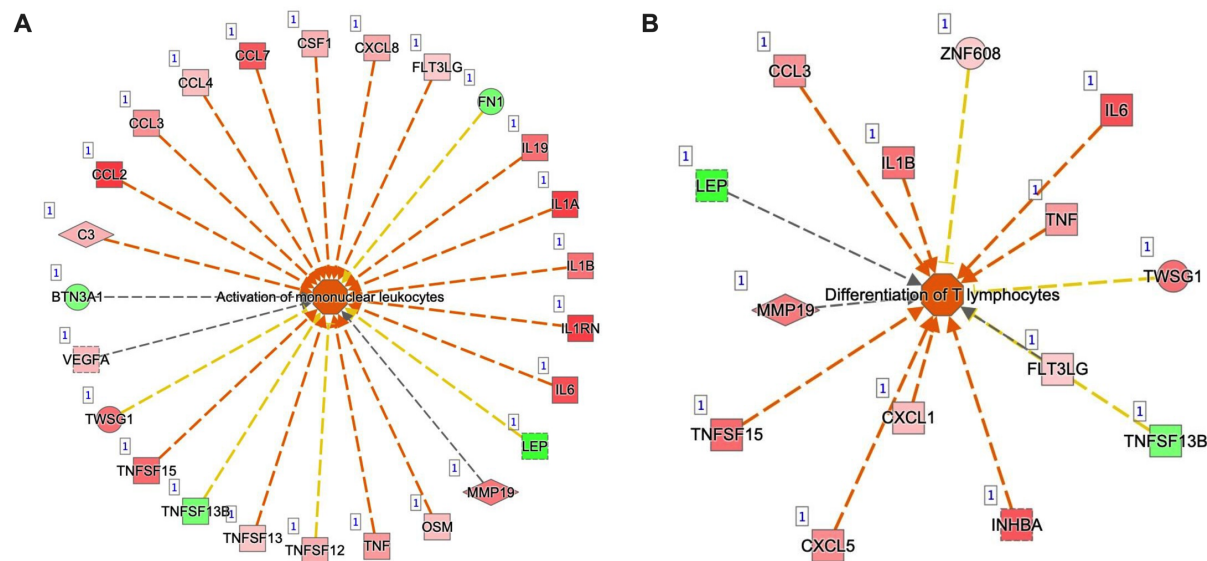


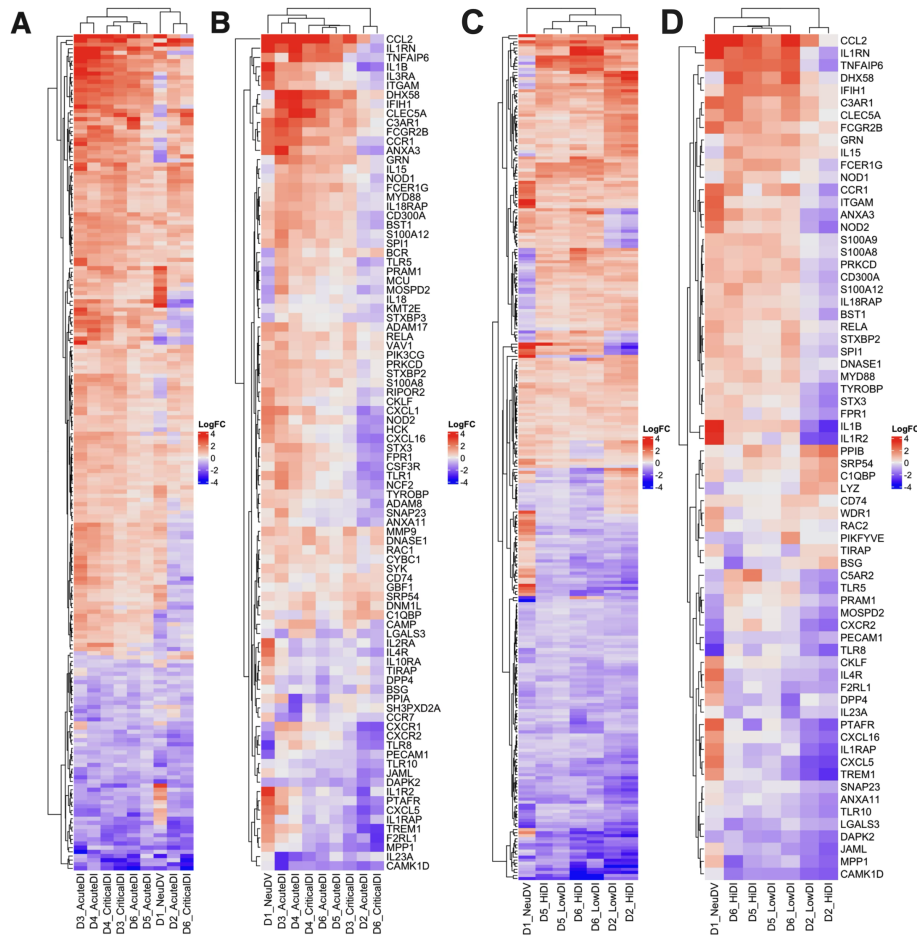
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81 **Supplementary Figure S9. IPA causal network of IL-6 signaling in DENV3-treated**
 82 **neutrophils.** IPA network illustrating IL-6 as a predicted activated upstream regulator and its
 83 downstream effects. Node colors represent gene expression changes (red: upregulated; green:
 84 downregulated; orange: activated regulator). Edge colors indicate predicted activation (orange),
 85 inhibition (blue), or inconsistent (yellow) relationships. Cellular compartments are annotated for
 86 context.

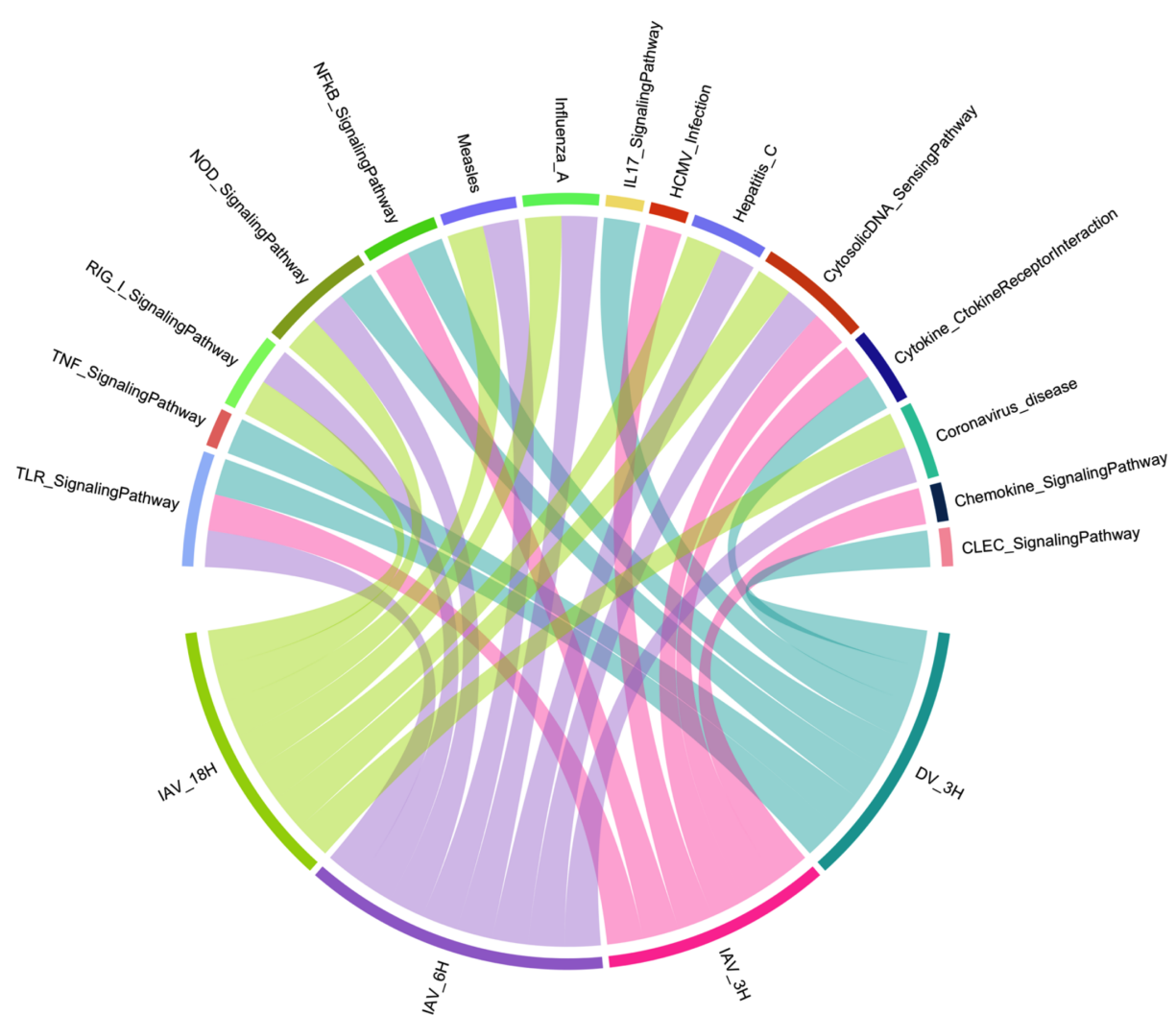


Supplementary Figure S10. IPA causal network of TNF signaling in DENV3-treated neutrophils. IPA network illustrating TNF as a predicted activated upstream regulator and its downstream molecular effects. Node colors show gene expression changes (red: upregulated; green: downregulated; orange: activated regulator). Edge colors indicate predicted activation (orange), inhibition (blue), or inconsistent (yellow) relationships. Cellular compartments are annotated for context.





Supplementary Figure S12. Dengue-neutrophil transcriptomic signatures reflect patient-level transcriptional responses. Pearson correlation analysis comparing gene expression profiles of DENV3-treated neutrophils (D1) with five publicly available dengue patient transcriptomic datasets (D2–D6). Clustering heatmaps demonstrate concordant transcriptional patterns, supporting that *ex vivo* dengue–neutrophil signatures recapitulate patient-level immune responses. Panels (A, C) show correlations based on shared differentially expressed genes (DEGs), whereas panels (B, D) show correlations using neutrophil-related DEGs. Disease categories include clinical phase (Acute and Critical) and disease severity classified as high disease index (HighDI) and low disease index (LowDI).



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117 **Supplementary Figure S13. Chord diagram illustrating shared signaling pathways among**
118 **viral infections.** Chord diagram showing the overlap of enriched signaling pathways between
119 DENV (DENV-3) and IAV infections. Connections represent pathways commonly activated
120 across viruses, including cytokine signaling, chemokine signaling, IL-17 signaling, TNF signaling,
121 NF-κB activation, and coronavirus-associated pathways. The width of each chord reflects the
122 extent of pathway overlap, highlighting conserved host immune responses to diverse viral
123 pathogens.

124 **Supplementary Table S1. Enrichment analysis results of dysregulated genes in DENV3-treated neutrophils.** FDR indicates the
125 false discovery rate. nGenes represents the number of genes mapped to each pathway, and pathway size indicates the total number of
126 genes in the pathway. Fold enrichment represents the enrichment magnitude.

	GO Term/KEGG	Group	FDR	nGenes	Pathway size	Fold enriched	Pathway
1	Biological process	Upregulated	2.1E-20	182	3329	2.03	Immune system process
2	Biological process	Upregulated	3.26E-20	91	977	3.13	Inflammatory response
3	Biological process	Upregulated	8.11E-18	153	2755	2.09	Response to external stimulus
4	Biological process	Upregulated	1.86E-17	272	7482	1.57	Signaling
5	Biological process	Upregulated	2.4E-17	271	7502	1.56	Cell communication
6	Biological process	Upregulated	4.06E-17	258	6949	1.59	Signal transduction
7	Biological process	Upregulated	9.01E-17	132	2241	2.19	Defense response
8	Biological process	Upregulated	1.2E-16	190	4417	1.81	Response to chemical
9	Biological process	Upregulated	1.41E-16	135	2468	2.15	Immune response
10	Biological process	Upregulated	7.39E-16	81	1011	2.87	Response to lipid
11	Biological process	Upregulated	1.66E-15	61	1581	3.47	G protein-coupled receptor signaling pathway
12	Biological process	Upregulated	7.48E-15	135	2398	2.05	Cellular response to chemical stimulus
13	Biological process	Upregulated	9.54E-15	334	10107	1.37	Response to stimulus
14	Biological process	Upregulated	2.66E-14	295	8428	1.43	Cellular response to stimulus
15	Biological process	Upregulated	1.52E-13	57	605	3.32	Cytokine-mediated signaling pathway
16	Biological process	Upregulated	1.52E-13	83	1067	2.57	Response to cytokine
17	Biological process	Upregulated	3.08E-13	83	1082	2.53	Response to peptide
18	Biological process	Upregulated	3.83E-13	111	1891	2.15	Response to other organism
19	Biological process	Upregulated	3.91E-13	111	1894	2.14	Response to external biotic stimulus

20	Biological process	Upregulated	1.14E-12	89	1185	2.37	Leukocyte activation
21	Biological process	Upregulated	1.9E-12	118	2079	2.03	Biological process involved in interspecies interaction between organisms
22	Biological process	Upregulated	2E-12	107	1772	2.13	Response to oxygen-containing compound
23	Biological process	Upregulated	2.76E-12	60	805	2.97	Response to bacterium
24	Biological process	Upregulated	3.7E-12	116	2090	2.03	Regulation of immune system process
25	Biological process	Upregulated	6.37E-12	264	8166	1.44	Multicellular organismal process
26	Biological process	Upregulated	8.13E-12	153	3355	1.77	Regulation of multicellular organismal process
27	Biological process	Upregulated	1.23E-11	58	679	2.94	Cellular response to lipid
28	Biological process	Upregulated	1.39E-11	44	399	3.58	Response to molecule of bacterial origin
29	Biological process	Upregulated	1.46E-11	73	966	2.53	Cellular response to cytokine stimulus
30	Biological process	Upregulated	1.91E-11	46	459	3.43	Leukocyte migration
31	Biological process	Upregulated	2.43E-11	92	1362	2.20	Cell activation
32	Biological process	Upregulated	2.74E-11	92	1570	2.20	Defense response to other organism
33	Biological process	Upregulated	2.87E-11	84	1276	2.30	Cellular response to oxygen-containing compound
34	Biological process	Upregulated	3.89E-11	85	1273	2.27	Regulation of response to external stimulus
35	Biological process	Upregulated	4.07E-11	42	377	3.59	Response to lipopolysaccharide
36	Biological process	Upregulated	5.61E-11	104	1931	2.04	Positive regulation of multicellular organismal process
37	Biological process	Upregulated	1.38E-10	92	1655	2.13	Cell migration
38	Biological process	Upregulated	1.39E-10	87	1796	2.19	Cell adhesion
39	Biological process	Upregulated	1.72E-10	44	454	3.31	Regulation of inflammatory response
40	Biological process	Upregulated	2.31E-10	82	1357	2.24	Locomotion
41	Biological process	Upregulated	2.52E-10	140	3099	1.75	Cell surface receptor signaling pathway
42	Biological process	Upregulated	2.52E-10	33	261	4.13	Cellular response to molecule of bacterial origin
43	Biological process	Upregulated	3.38E-10	32	251	4.19	Cellular response to lipopolysaccharide
44	Biological process	Upregulated	3.75E-10	85	1454	2.17	Defense response to symbiont

45	Biological process	Upregulated	9.83E-10	71	1098	2.34	Regulation of cell motility
46	Biological process	Upregulated	1.37E-09	95	1921	2.01	Cell motility
47	Biological process	Upregulated	1.44E-09	97	1621	1.99	Regulation of apoptotic process
48	Biological process	Upregulated	1.55E-09	72	1146	2.30	Regulation of locomotion
49	Biological process	Upregulated	1.74E-09	118	2120	1.82	Apoptotic process
50	Biological process	Upregulated	1.97E-09	99	1674	1.96	Regulation of programmed cell death
51	Biological process	Upregulated	2.23E-09	31	278	4.01	Myeloid leukocyte migration
52	Biological process	Upregulated	2.24E-09	68	1035	2.34	Regulation of cell migration
53	Biological process	Upregulated	2.34E-09	161	3241	1.61	Intracellular signal transduction
54	Biological process	Upregulated	2.97E-09	86	1380	2.07	Positive regulation of immune system process
55	Biological process	Upregulated	2.97E-09	94	1851	1.99	Regulation of cell population proliferation
56	Biological process	Upregulated	3.2E-09	63	1187	2.42	Cell-cell adhesion
57	Biological process	Upregulated	3.95E-09	120	2197	1.78	Programmed cell death
58	Biological process	Upregulated	4.31E-09	120	2201	1.78	Cell death
59	Biological process	Upregulated	4.33E-09	50	655	2.75	Positive regulation of locomotion
60	Biological process	Upregulated	4.6E-09	63	959	2.40	Response to organic cyclic compound
61	Biological process	Upregulated	4.62E-09	84	1531	2.07	Regulation of multicellular organismal development
62	Biological process	Upregulated	4.7E-09	25	177	4.69	Granulocyte migration
63	Biological process	Upregulated	4.7E-09	113	2085	1.82	Intracellular signaling cassette
64	Biological process	Upregulated	4.71E-09	71	1286	2.25	Anatomical structure formation involved in morphogenesis
65	Biological process	Upregulated	5.07E-09	193	4704	1.50	Regulation of response to stimulus
66	Biological process	Upregulated	5.51E-09	49	637	2.76	Positive regulation of cell motility
67	Biological process	Upregulated	5.53E-09	196	4545	1.49	Response to stress
68	Biological process	Upregulated	5.94E-09	30	274	3.93	Leukocyte chemotaxis
69	Biological process	Upregulated	6.35E-09	18	117	6.50	Response to chemokine

70	Biological process	Upregulated	6.35E-09	18	117	6.50	Cellular response to chemokine
71	Biological process	Upregulated	7.97E-09	58	784	2.47	Positive regulation of response to external stimulus
72	Biological process	Upregulated	8.16E-09	70	1220	2.23	Negative regulation of multicellular organismal process
73	Biological process	Upregulated	8.16E-09	33	288	3.59	Cellular response to biotic stimulus
74	Biological process	Upregulated	8.59E-09	18	144	6.38	Phospholipase c-activating g protein-coupled receptor signaling pathway
75	Biological process	Upregulated	9.5E-09	48	609	2.74	Positive regulation of cell migration
76	Biological process	Upregulated	9.67E-09	68	983	2.25	Regulation of defense response
77	Biological process	Upregulated	1.07E-08	55	715	2.52	Regulation of leukocyte activation
78	Biological process	Upregulated	1.07E-08	105	2185	1.84	Cell population proliferation
79	Biological process	Upregulated	1.38E-08	22	147	5.01	Granulocyte chemotaxis
80	Biological process	Upregulated	1.6E-08	33	369	3.49	Cell chemotaxis
81	Biological process	Upregulated	1.71E-08	40	522	3.03	Chemotaxis
82	Biological process	Upregulated	1.71E-08	40	524	3.03	Taxis
83	Biological process	Upregulated	1.75E-08	120	2868	1.73	Anatomical structure morphogenesis
84	Biological process	Upregulated	2.38E-08	78	1449	2.06	Positive regulation of developmental process
85	Biological process	Upregulated	2.5E-08	129	2719	1.68	Positive regulation of response to stimulus
86	Biological process	Upregulated	2.61E-08	65	983	2.25	Regulation of cytokine production
87	Biological process	Upregulated	2.7E-08	16	108	6.80	Chemokine-mediated signaling pathway
88	Biological process	Upregulated	2.97E-08	65	990	2.24	Cytokine production
89	Biological process	Upregulated	3.76E-08	165	3758	1.54	Regulation of cell communication
90	Biological process	Upregulated	4.1E-08	56	788	2.40	Regulation of cell activation
91	Biological process	Upregulated	4.15E-08	55	728	2.42	T cell activation
92	Biological process	Upregulated	4.56E-08	165	3753	1.53	Regulation of signaling
93	Biological process	Upregulated	4.56E-08	263	6941	1.33	Positive regulation of biological process
94	Biological process	Upregulated	5.82E-08	44	546	2.72	Leukocyte cell-cell adhesion

95	Biological process	Upregulated	6.15E-08	68	987	2.15	Lymphocyte activation
96	Biological process	Upregulated	7.15E-08	30	316	3.52	Regulation of angiogenesis
97	Biological process	Upregulated	7.51E-08	51	615	2.48	Positive regulation of programmed cell death
98	Biological process	Upregulated	7.51E-08	22	172	4.58	Positive regulation of angiogenesis
99	Biological process	Upregulated	9.16E-08	46	653	2.61	Regulation of cell-cell adhesion
1	Cellular component	Upregulated	2.5E-18	232	7151	1.70	Cell periphery
2	Cellular component	Upregulated	4.05E-18	222	6639	1.72	Plasma membrane
3	Cellular component	Upregulated	3.32E-07	53	1085	2.41	Cell surface
4	Cellular component	Upregulated	1.71E-05	16	105	4.79	Tertiary granule membrane
5	Cellular component	Upregulated	2.43E-05	145	4675	1.47	Extracellular region
6	Cellular component	Upregulated	3.7E-05	316	11335	1.21	Membrane
7	Cellular component	Upregulated	9.34E-05	125	3619	1.49	Extracellular space
8	Cellular component	Upregulated	1.23E-03	21	208	2.80	Tertiary granule
9	Cellular component	Upregulated	2.62E-03	26	485	2.35	External side of plasma membrane
10	Cellular component	Upregulated	4.33E-03	21	329	2.54	Membrane raft
11	Cellular component	Upregulated	4.72E-03	21	331	2.51	Membrane microdomain
12	Cellular component	Upregulated	1.02E-02	21	433	2.36	Receptor complex
13	Cellular component	Upregulated	1.17E-02	19	211	2.45	Specific granule
14	Cellular component	Upregulated	1.54E-02	13	121	2.98	Specific granule membrane
15	Cellular component	Upregulated	3.5E-02	49	1030	1.58	Secretory granule
16	Cellular component	Upregulated	5.17E-02	17	329	2.25	Basal part of cell
17	Cellular component	Upregulated	5.49E-02	17	595	2.21	External encapsulating structure
18	Cellular component	Upregulated	5.49E-02	24	368	1.90	Secretory granule membrane
19	Cellular component	Upregulated	5.49E-02	17	594	2.21	Extracellular matrix
20	Cellular component	Upregulated	5.49E-02	9	129	3.19	Plasma membrane raft

21	Cellular component	Upregulated	6.75E-02	3	6	9.74	Ripoptosome
22	Cellular component	Upregulated	6.76E-02	2	12	19.47	Sodium:potassium-exchanging atpase complex
23	Cellular component	Upregulated	6.76E-02	2	3	19.47	Rough endoplasmic reticulum lumen
24	Cellular component	Upregulated	7.25E-02	110	2941	1.28	Cytoplasmic vesicle
25	Cellular component	Upregulated	7.38E-02	110	2947	1.27	Intracellular vesicle
26	Cellular component	Upregulated	7.72E-02	34	907	1.63	Side of membrane
27	Cellular component	Upregulated	8.43E-02	15	310	2.16	Basal plasma membrane
28	Cellular component	Upregulated	8.82E-02	52	1234	1.45	Secretory vesicle
1	Molecular function	Upregulated	5.78E-17	61	1705	3.77	Transmembrane signaling receptor activity
2	Molecular function	Upregulated	9.85E-17	30	296	7.63	Cytokine activity
3	Molecular function	Upregulated	3.36E-16	40	626	5.25	Receptor ligand activity
4	Molecular function	Upregulated	8.5E-16	40	639	5.08	Signaling receptor activator activity
5	Molecular function	Upregulated	8.5E-16	71	2007	3.08	Signaling receptor activity
6	Molecular function	Upregulated	8.5E-16	71	2007	3.08	Molecular transducer activity
7	Molecular function	Upregulated	4.63E-15	40	688	4.80	Signaling receptor regulator activity
8	Molecular function	Upregulated	5.23E-13	32	1085	5.22	G protein-coupled receptor activity
9	Molecular function	Upregulated	2.57E-12	14	68	13.70	Chemokine activity
10	Molecular function	Upregulated	7.82E-12	32	334	4.74	Cytokine receptor binding
11	Molecular function	Upregulated	4.92E-09	14	105	9.13	Chemokine receptor binding
12	Molecular function	Upregulated	3.37E-08	107	2457	1.80	Molecular function regulator activity
13	Molecular function	Upregulated	8.5E-08	73	1772	2.08	Signaling receptor binding
14	Molecular function	Upregulated	9.62E-08	66	1321	2.17	Molecular function activator activity
15	Molecular function	Upregulated	5.96E-07	23	343	4.02	G protein-coupled receptor binding
16	Molecular function	Upregulated	2.81E-05	8	77	9.79	Ccr chemokine receptor binding
17	Molecular function	Upregulated	1.13E-03	5	15	12.23	G protein-coupled purinergic nucleotide receptor activity

18	Molecular function	Upregulated	2.54E-03	14	272	3.47	Glycosaminoglycan binding
19	Molecular function	Upregulated	2.72E-03	15	276	3.26	Immune receptor activity
20	Molecular function	Upregulated	5.32E-03	4	12	13.05	Ccr1 chemokine receptor binding
21	Molecular function	Upregulated	6.07E-03	5	22	8.90	Purinergic nucleotide receptor activity
22	Molecular function	Upregulated	6.07E-03	5	22	8.90	Nucleotide receptor activity
23	Molecular function	Upregulated	6.07E-03	5	18	8.90	Cxcr chemokine receptor binding
24	Molecular function	Upregulated	6.32E-03	3	23	19.57	G protein-coupled serotonin receptor activity
25	Molecular function	Upregulated	8.6E-03	44	902	1.75	Lipid binding
26	Molecular function	Upregulated	9.55E-03	9	86	4.19	Cargo receptor activity
27	Molecular function	Upregulated	1.04E-02	7	59	5.27	E-box binding
28	Molecular function	Upregulated	1.53E-02	8	71	4.35	Tumor necrosis factor receptor superfamily binding
29	Molecular function	Upregulated	1.6E-02	10	106	3.56	Cytokine receptor activity
30	Molecular function	Upregulated	1.85E-02	6	132	5.59	Potassium channel activity
31	Molecular function	Upregulated	1.88E-02	3	6	14.68	Histamine receptor activity
32	Molecular function	Upregulated	2.96E-02	6	108	5.11	Serine-type endopeptidase inhibitor activity
33	Molecular function	Upregulated	3.83E-02	4	17	7.83	Interleukin-1 receptor binding
34	Molecular function	Upregulated	4.13E-02	3	41	11.74	G protein-coupled amine receptor activity
35	Molecular function	Upregulated	4.14E-02	5	106	5.76	Voltage-gated potassium channel activity
36	Molecular function	Upregulated	4.47E-02	7	80	4.03	Monocarboxylic acid binding
37	Molecular function	Upregulated	4.69E-02	8	98	3.56	Amyloid-beta binding
38	Molecular function	Upregulated	4.69E-02	4	16	7.12	Low-density lipoprotein particle receptor activity
39	Molecular function	Upregulated	4.69E-02	6	52	4.52	Tumor necrosis factor receptor binding
40	Molecular function	Upregulated	4.69E-02	7	171	3.91	Potassium ion transmembrane transporter activity
41	Molecular function	Upregulated	4.69E-02	4	17	7.12	1-phosphatidylinositol-3-kinase regulator activity
42	Molecular function	Upregulated	4.84E-02	8	166	3.48	Growth factor activity

43	Molecular function	Upregulated	5.61E-02	12	125	2.53	Transcription coregulator binding
44	Molecular function	Upregulated	5.61E-02	3	6	9.79	Lipopolysaccharide immune receptor activity
45	Molecular function	Upregulated	5.61E-02	2	3	19.57	Arachidonate 5-lipoxygenase activity
46	Molecular function	Upregulated	5.61E-02	3	7	9.79	Interleukin-1 receptor activity
47	Molecular function	Upregulated	5.61E-02	2	3	19.57	Interleukin-3 receptor activity
48	Molecular function	Upregulated	5.61E-02	3	28	9.79	Inward rectifier potassium channel activity
49	Molecular function	Upregulated	5.61E-02	61	1475	1.43	Enzyme regulator activity
50	Molecular function	Upregulated	5.61E-02	3	20	9.79	Transmembrane receptor protein tyrosine kinase activator activity
51	Molecular function	Upregulated	5.61E-02	2	13	19.57	Death receptor agonist activity
52	Molecular function	Upregulated	5.61E-02	2	3	19.57	G protein-coupled utp receptor activity
53	Molecular function	Upregulated	5.61E-02	2	2	19.57	Nicotinic acid receptor activity
54	Molecular function	Upregulated	5.61E-02	3	6	9.79	Cysteine-type endopeptidase activity involved in apoptotic signaling pathway
55	Molecular function	Upregulated	6.8E-02	4	19	6.02	Lipoprotein particle receptor activity
56	Molecular function	Upregulated	6.8E-02	25	598	1.79	Molecular function inhibitor activity
57	Molecular function	Upregulated	7.87E-02	9	91	2.84	Cysteine-type endopeptidase activity
58	Molecular function	Upregulated	7.87E-02	3	17	8.39	Peptidoglycan binding
59	Molecular function	Upregulated	9.31E-02	17	297	2.00	Dna-binding transcription repressor activity
60	Molecular function	Upregulated	9.75E-02	8	199	2.95	Heparin binding
61	Molecular function	Downregulated	5.15E-02	5	29	10.71	Phosphatidylinositol bisphosphate phosphatase activity
62	Molecular function	Downregulated	6.25E-02	5	35	9.00	Phosphatidylinositol phosphate phosphatase activity
1	KEGG	Upregulated	6.51E-08	42	294	2.72	Cytokine-cytokine receptor interaction
2	KEGG	Upregulated	2.84E-06	22	102	3.55	Amoebiasis
3	KEGG	Upregulated	6.81E-06	31	112	2.70	TNF signaling pathway
4	KEGG	Upregulated	1.33E-05	24	93	3.03	IL-17 signaling pathway
5	KEGG	Upregulated	2.16E-05	21	92	3.18	Rheumatoid arthritis

6	KEGG	Upregulated	2.16E-05	43	214	2.14	Lipid and atherosclerosis
7	KEGG	Upregulated	3.05E-05	27	104	2.66	NF-kappa B signaling pathway
8	KEGG	Upregulated	1.31E-04	25	109	2.56	HIF-1 signaling pathway
9	KEGG	Upregulated	1.31E-04	23	100	2.68	AGE-RAGE signaling pathway in diabetic complications
10	KEGG	Upregulated	1.31E-04	18	57	3.10	Legionellosis
11	KEGG	Upregulated	1.82E-04	28	138	2.36	Fluid shear stress and atherosclerosis
12	KEGG	Upregulated	2.14E-04	18	99	2.96	Viral protein interaction with cytokine and cytokine receptor
13	KEGG	Upregulated	2.14E-04	19	76	2.88	Pertussis
14	KEGG	Upregulated	3.01E-04	47	249	1.84	Salmonella infection
15	KEGG	Upregulated	3.01E-04	22	112	2.56	Toxoplasmosis
16	KEGG	Upregulated	3.09E-04	27	126	2.30	Osteoclast differentiation
17	KEGG	Upregulated	3.57E-04	20	99	2.66	Hematopoietic cell lineage
18	KEGG	Upregulated	7.07E-04	32	179	2.04	Tuberculosis
19	KEGG	Upregulated	9.59E-04	25	151	2.23	Phagosome
20	KEGG	Upregulated	1.21E-03	33	183	1.95	NOD-like receptor signaling pathway
21	KEGG	Upregulated	2.45E-03	28	136	2.00	Apoptosis
22	KEGG	Upregulated	2.45E-03	23	162	2.18	JAK-STAT signaling pathway
23	KEGG	Upregulated	2.75E-03	62	530	1.54	Pathways in cancer
24	KEGG	Upregulated	2.89E-03	17	98	2.48	Inflammatory mediator regulation of TRP channels
25	KEGG	Upregulated	2.92E-03	33	197	1.85	Pathogenic Escherichia coli infection
26	KEGG	Upregulated	3.01E-03	19	362	2.32	Neuroactive ligand-receptor interaction
27	KEGG	Upregulated	3.7E-03	20	101	2.23	Chagas disease
28	KEGG	Upregulated	3.83E-03	11	85	3.09	Complement and coagulation cascades
29	KEGG	Upregulated	8.45E-03	29	193	1.82	Transcriptional misregulation in cancer
30	KEGG	Upregulated	8.92E-03	39	354	1.64	PI3K-Akt signaling pathway

31	KEGG	Upregulated	8.92E-03	32	202	1.74	Epstein-Barr virus infection
32	KEGG	Upregulated	8.92E-03	19	89	2.12	PD-L1 expression and PD-1 checkpoint pathway in cancer
33	KEGG	Upregulated	1.07E-02	40	246	1.61	Shigellosis
34	KEGG	Upregulated	1.07E-02	12	65	2.60	Inflammatory bowel disease
35	KEGG	Upregulated	1.36E-02	20	108	1.99	Th17 cell differentiation
36	KEGG	Upregulated	1.43E-02	27	137	1.78	Yersinia infection
37	KEGG	Upregulated	1.47E-02	14	76	2.31	Leishmaniasis
38	KEGG	Upregulated	1.5E-02	11	41	2.60	Ferroptosis
39	KEGG	Upregulated	1.5E-02	31	194	1.69	Kaposi sarcoma-associated herpesvirus infection
40	KEGG	Upregulated	1.67E-02	24	139	1.82	Measles
41	KEGG	Upregulated	2.26E-02	17	103	2.01	Toll-like receptor signaling pathway
42	KEGG	Upregulated	2.26E-02	25	171	1.75	Influenza A
43	KEGG	Upregulated	2.71E-02	19	104	1.89	C-type lectin receptor signaling pathway
44	KEGG	Upregulated	2.88E-02	36	294	1.55	MAPK signaling pathway
45	KEGG	Upregulated	3.5E-02	26	162	1.67	Hepatitis B
46	KEGG	Upregulated	3.62E-02	23	159	1.73	Necroptosis
47	KEGG	Upregulated	4.23E-02	10	76	2.37	Gastric acid secretion
48	KEGG	Upregulated	4.6E-02	8	94	2.64	Staphylococcus aureus infection

128 **Supplementary Table S2. Gene set enrichment analysis results of dysregulated genes in DENV3-treated neutrophils.** adj.Pval
129 indicates the adjusted p-value. nGenes represents the number of genes mapped to each pathway, and NES indicates the normalized
130 enrichment score.

	GO Term/KEGG	Direction	adj.Pval	nGenes	NES	GSEA analysis: DV vs MOCK Pathways
2	Biological process	Upregulated	5.1E-04	17	0.8271	Liver morphogenesis
3	Biological process	Upregulated	6.2E-04	6	0.9510	Negative regulation of collagen metabolic process
4	Biological process	Upregulated	7.5E-04	16	0.8336	Hepatocyte proliferation
5	Biological process	Upregulated	7.5E-04	16	0.8336	Epithelial cell proliferation involved in liver morphogenesis
6	Biological process	Upregulated	7.8E-04	6	0.9487	Positive regulation of neutrophil activation
7	Biological process	Upregulated	2.3E-03	7	0.9180	Immature T cell proliferation
8	Biological process	Upregulated	2.3E-03	7	0.9180	Immature T cell proliferation in thymus
9	Biological process	Upregulated	2.3E-03	7	0.9180	Regulation of immature T cell proliferation
10	Biological process	Upregulated	2.3E-03	7	0.9180	Regulation of immature T cell proliferation in thymus
11	Biological process	Upregulated	2.4E-03	9	0.8934	Eosinophil chemotaxis
12	Biological process	Upregulated	3.4E-03	6	0.9284	Regulation of heat generation
13	Biological process	Upregulated	3.8E-03	8	0.8952	Regulation of vascular wound healing
14	Biological process	Upregulated	4.3E-03	5	0.9598	Negative regulation of collagen biosynthetic process
15	Biological process	Upregulated	4.6E-03	7	0.9089	Positive regulation of hepatocyte proliferation
16	Biological process	Upregulated	5.1E-03	9	0.8773	Heat generation
17	Biological process	Upregulated	5.3E-03	6	0.9184	Negative regulation of lipoprotein particle clearance
18	Biological process	Upregulated	7.5E-03	13	0.8058	Vascular wound healing
19	Biological process	Upregulated	8.5E-03	11	0.8234	Regulation of vesicle fusion
20	Biological process	Upregulated	8.6E-03	6	0.9075	Fever generation

1	Biological process	Downregulated	1.1E-03	11	-0.8309	Regulation of natural killer cell proliferation
1	Cellular component	Upregulated	6E-07	1634	0.3675	Extracellular space
2	Cellular component	Upregulated	6E-07	1944	0.3568	Extracellular region
3	Cellular component	Upregulated	2.1E-06	640	0.4228	Intrinsic component of plasma membrane
4	Cellular component	Upregulated	5.6E-05	414	0.4412	Cell surface
5	Cellular component	Upregulated	6.4E-05	610	0.4092	Integral component of plasma membrane
6	Cellular component	Upregulated	3.8E-03	146	0.5015	Tertiary granule
7	Cellular component	Upregulated	3.8E-03	176	0.4843	Ribosomal subunit
8	Cellular component	Upregulated	3.8E-03	1321	0.3416	Extracellular vesicle
9	Cellular component	Upregulated	4.3E-03	1322	0.3395	Extracellular organelle
10	Cellular component	Upregulated	4.3E-03	1322	0.3395	Extracellular membrane-bounded organelle
11	Cellular component	Upregulated	4.8E-03	65	0.5964	Tertiary granule membrane
12	Cellular component	Upregulated	5.3E-03	1313	0.3373	Extracellular exosome
1	Molecular function	Upregulated	4.3E-11	76	0.7614	Cytokine activity
2	Molecular function	Upregulated	2.6E-10	131	0.6573	Receptor ligand activity
3	Molecular function	Upregulated	2.6E-10	136	0.6521	Signaling receptor activator activity
4	Molecular function	Upregulated	2.6E-10	132	0.6499	Cytokine receptor binding
5	Molecular function	Upregulated	2.6E-10	143	0.6431	Signaling receptor regulator activity
6	Molecular function	Upregulated	6.5E-08	322	0.5037	Transmembrane signaling receptor activity
7	Molecular function	Upregulated	6.5E-08	448	0.4684	Signaling receptor activity
8	Molecular function	Upregulated	6.5E-08	448	0.4684	Molecular transducer activity
9	Molecular function	Upregulated	1.1E-06	662	0.4162	Signaling receptor binding
10	Molecular function	Upregulated	8.1E-06	20	0.8627	Chemokine activity
11	Molecular function	Upregulated	1.3E-05	120	0.5848	G protein-coupled receptor activity

12	Molecular function	Upregulated	1.5E-04	1017	0.3666	Molecular function regulator activity
13	Molecular function	Upregulated	3E-04	110	0.5728	G protein-coupled receptor binding
14	Molecular function	Upregulated	5.6E-04	30	0.7576	Chemokine receptor binding
15	Molecular function	Upregulated	3.6E-03	147	0.4938	Structural constituent of ribosome
1	KEGG	Upregulated	3.5E-06	117	0.6074	Cytokine-cytokine receptor interaction
2	KEGG	Upregulated	1.1E-05	60	0.6888	IL-17 signaling pathway
3	KEGG	Upregulated	1.1E-05	77	0.6457	NF-kappa B signaling pathway
4	KEGG	Upregulated	7.9E-05	50	0.6874	Rheumatoid arthritis
5	KEGG	Upregulated	7.9E-05	50	0.6779	Pertussis
6	KEGG	Upregulated	7.9E-05	65	0.6536	Toxoplasmosis
7	KEGG	Upregulated	7.9E-05	87	0.6108	TNF signaling pathway
8	KEGG	Upregulated	1E-04	108	0.5630	Influenza A
9	KEGG	Upregulated	2.2E-04	47	0.6804	Amoebiasis
10	KEGG	Upregulated	2.2E-04	89	0.5808	Osteoclast differentiation
11	KEGG	Upregulated	2.2E-04	119	0.5437	Tuberculosis
12	KEGG	Upregulated	3.9E-04	46	0.6643	Viral protein interaction with cytokine and cytokine receptor
13	KEGG	Upregulated	3.9E-04	100	0.5550	Measles
14	KEGG	Upregulated	4.4E-04	44	0.6752	Legionellosis
15	KEGG	Upregulated	4.9E-04	80	0.5705	JAK-STAT signaling pathway
16	KEGG	Upregulated	6E-04	65	0.6143	AGE-RAGE signaling pathway in diabetic complications
17	KEGG	Upregulated	1.5E-03	68	0.5887	Chagas disease
18	KEGG	Upregulated	1.9E-03	10	0.8739	Graft-versus-host disease
19	KEGG	Upregulated	3.4E-03	57	0.5843	Hematopoietic cell lineage
20	KEGG	Upregulated	7E-03	46	0.6018	Leishmaniasis

132 **Supplementary Table S3. Pearson correlation analysis of shared differentially expressed genes (DEGs) between DENV3-treated**
133 **neutrophils and dengue patient transcriptomic datasets.** Correlation coefficients represent similarity of gene expression profiles
134 across datasets from different days of illness (DI). Statistical significance is indicated as $*p < 0.05$, $**p < 0.01$ and $***p < 0.001$.

Shared DEGs		D1_NeuDV	D2_AcuteDI	D3_AcuteDI	D4_AcuteDI	D5_AcuteDI	D6_AcuteDI	D3_CriticalDI	D4_CriticalDI	D6_CriticalDI
	D1_NeuDV	1.000	0.222**	0.312***	0.326***	0.338***	0.320***	0.298***	0.340***	0.207**
	D2_AcuteDI	0.222	1.000	0.555***	0.519***	0.640***	0.606***	0.825***	0.689***	0.828***
	D3_AcuteDI	0.312	0.555	1.000	0.890***	0.846***	0.854***	0.807***	0.854***	0.510***
	D4_AcuteDI	0.326	0.519	0.890	1.000	0.839***	0.867***	0.762***	0.916***	0.453***
	D5_AcuteDI	0.338	0.640	0.846	0.839	1.000	0.855***	0.811***	0.853***	0.561***
	D6_AcuteDI	0.320	0.606	0.854	0.867	0.855	1.000	0.845***	0.894***	0.678***
	D3_CriticalDI	0.298	0.825	0.807	0.762	0.811	0.845	1.000	0.920***	0.839***
	D4_CriticalDI	0.340	0.689	0.854	0.916	0.853	0.894	0.920	1.000	0.681***
	D6_CriticalDI	0.207	0.828	0.510	0.453	0.561	0.678	0.839	0.681	1.000
.										
Neutrophil-related DEGs		D1_NeuDV	D2_AcuteDI	D3_AcuteDI	D4_AcuteDI	D5_AcuteDI	D6_AcuteDI	D3_CriticalDI	D4_CriticalDI	D6_CriticalDI
	D1_NeuDV	1.000	-0.026	0.421***	0.394***	0.358***	0.366***	0.225*	0.314**	-0.099
	D2_AcuteDI	-0.026	1.000	0.189	0.238*	0.440***	0.354***	0.694***	0.475***	0.733***
	D3_AcuteDI	0.421	0.189	1.000	0.810***	0.686***	0.777***	0.649***	0.732***	0.030
	D4_AcuteDI	0.394	0.238	0.810	1.000	0.761***	0.893***	0.620***	0.881***	0.042
	D5_AcuteDI	0.358	0.440	0.686	0.761	1.000	0.871***	0.681***	0.801***	0.266*
	D6_AcuteDI	0.366	0.354	0.777	0.893	0.871	1.000	0.733***	0.876***	0.284**
	D3_CriticalDI	0.225	0.694	0.649	0.620	0.681	0.733	1.000	0.794***	0.610***

	D4_CriticalDI	0.314	0.475	0.732	0.881	0.801	0.876	0.794	1.000	0.291**
	D6_CriticalDI	-0.099	0.733	0.030	0.042	0.266	0.284	0.610	0.291	1.000
	.									
Shared DEGs		D1_NeuDV	D2_LowDI	D5_LowDI	D6_LowDI	D2_HiDI	D5_HiDI	D6_HiDI		
	D1_NeuDV	1.000	0.250***	0.320***	0.278***	0.222***	0.326***	0.232***		
	D2_LowDI	0.250	1.000	0.743***	0.688***	0.974***	0.733***	0.665***		
	D5_LowDI	0.320	0.743	1.000	0.881***	0.651***	0.970***	0.845***		
	D6_LowDI	0.278	0.688	0.881	1.000	0.614***	0.875***	0.927***		
	D2_HiDI	0.222	0.974	0.651	0.614	1.000	0.655***	0.589***		
	D5_HiDI	0.326	0.733	0.970	0.875	0.655	1.000	0.835***		
	D6_HiDI	0.232	0.665	0.845	0.927	0.589	0.835	1.000		
	.									
Neutrophil-related DEGs		D1_NeuDV	D2_LowDI	D5_LowDI	D6_LowDI	D2_HiDI	D5_HiDI	D6_HiDI		
	D1_NeuDV	1.000	0.032	0.383**	0.395***	-0.142	0.324**	0.390***		
	D2_LowDI	0.032	1.000	0.552***	0.536***	0.911***	0.537***	0.420***		
	D5_LowDI	0.383**	0.552***	1.000	0.795***	0.312**	0.841***	0.840***		
	D6_LowDI	0.395***	0.536***	0.795***	1.000	0.283*	0.756***	0.816***		
	D2_HiDI	-0.142	0.911***	0.312**	0.283*	1.000	0.359**	0.133		
	D5_HiDI	0.324**	0.537***	0.841***	0.756***	0.359**	1.000	0.806***		
	D6_HiDI	0.390***	0.420***	0.840***	0.816***	0.133	0.806***	1.000		