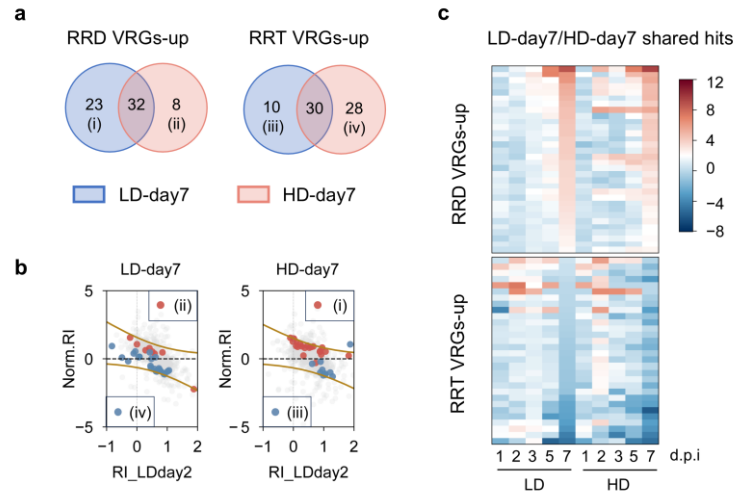


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2 Figure S1 Varied response regression index (RI) value for diverse genes in reference group.

3



4

5 **Figure S2 Identification of late-stage associated host genes via the response-regression**

6 **model. (a)** Venn plots showing counts of RRD and RRT genes at day 7 in LD and HD groups.

7 VRGs-up from the LD-day3 model group were included for response-regression analysis. **(b)**

8 Distribution of RRD/RRT genes uniquely detected at day7 in LD and HD groups in the

9 counterpart plots. **(c)** Heatmap of overlapping day7 RRD/RRT genes from LD and HD groups,

10 generated from log₂FC values in mouse lung tissues across sequential IAV infection time points.

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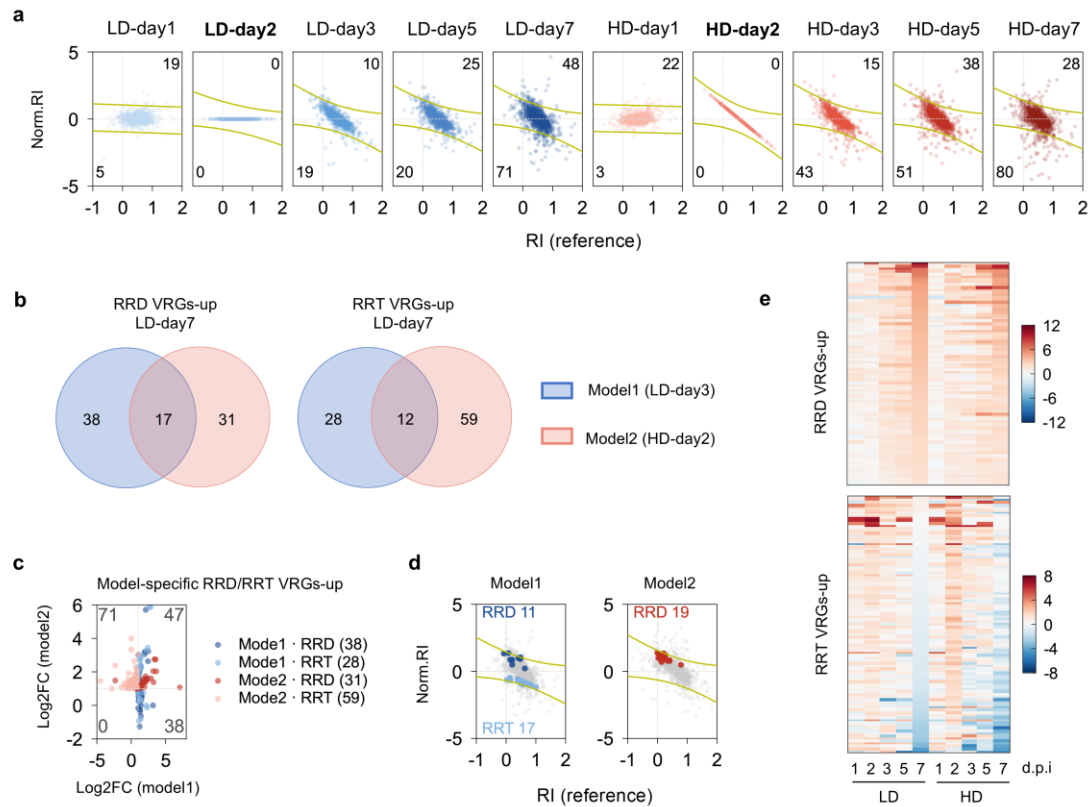


Figure S3 Robustness evaluation of the response-regression-model-based transcriptomic algorithm. (a) Screening of LD-day3 derived VRGs-up bearing RRD/RRT from HD day-7 transcriptomic profiles. HD-day2 and LD-day2 datasets were set as the model and reference groups, respectively. (b) Venn diagrams showing gene counts with RRD/RRT identified in HD day-7 under alternative model-group configurations. (c) Comparison of VRGs-up derived from LD-day3 and those from HD-day2. (d) Distribution of RRD/RRT VRGs-up uniquely detected by different model-group setups in the counterpart plots. (e) Heatmaps of HD-day7 RRD/RRT VRGs-up constructed using lung log₂FC values across sequential IAV infection time points. Hit genes from varied model-group configurations were pooled for integrative analysis.

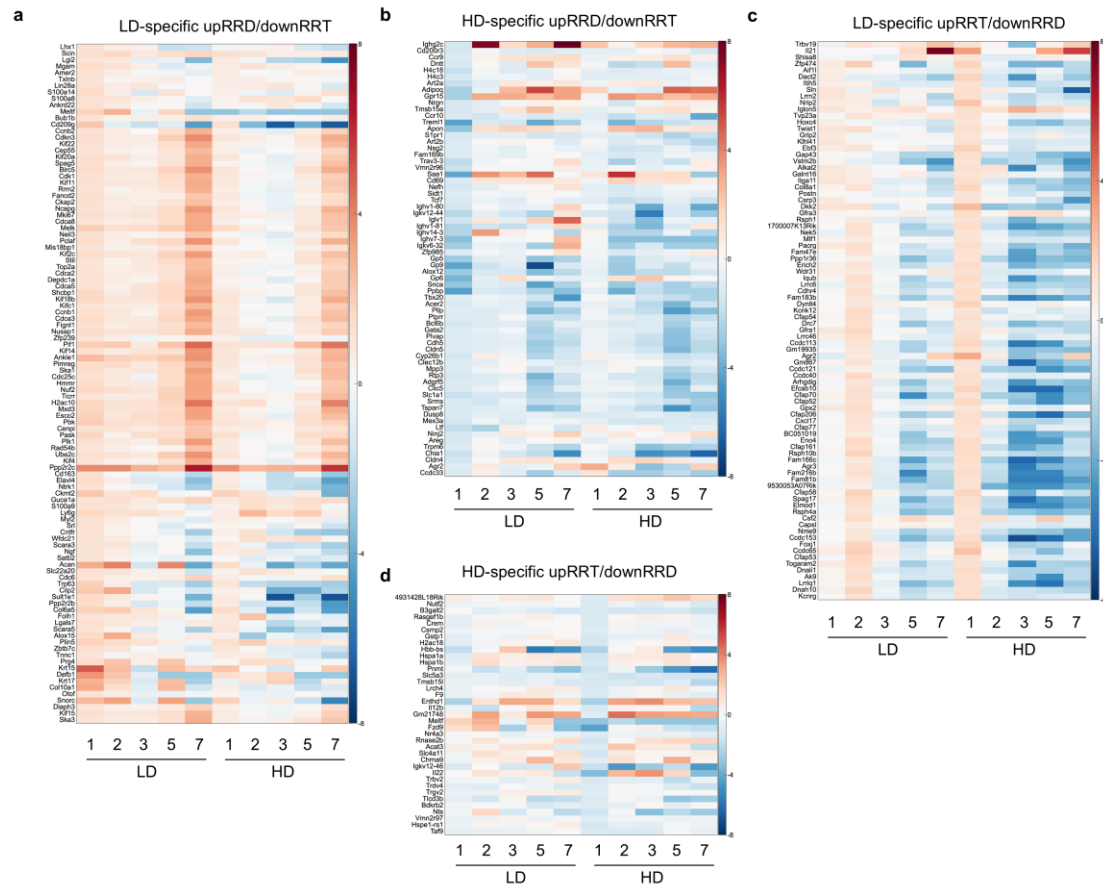


Figure S4 Heatmaps showing dynamic expression of RRD/RRT genes identified at LD-day1 or HD-day1. (a) LD-day1-specific RRD VRGs-up and RRT VRGs-down. (b) HD-day1-specific RRD VRGs-up and RRT VRGs-down. (c) LD-day1-specific RRT VRGs-up and RRD VRGs-down. (d) HD-day1-specific RRT VRGs-up and RRD VRGs-down. Individual gene symbols are annotated on the left.

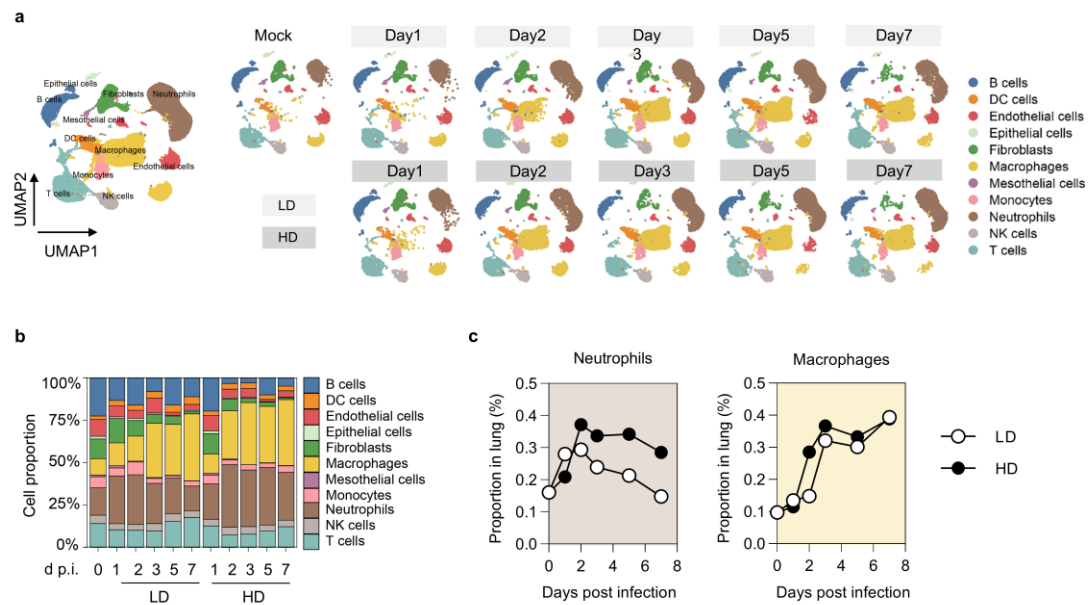


Figure S5 Dynamic comparison of immune cell abundance in LD and HD IAV-infected

mice. (a) Cell-type annotation of scRNA-seq data from lung tissues of IAV-infected mice. **(b)**

Temporal shifts in the proportions of distinct cell populations in IAV-infected mouse lungs.

(c) Abundance kinetics of innate immune neutrophils and macrophages in IAV-infected

mouse lungs.

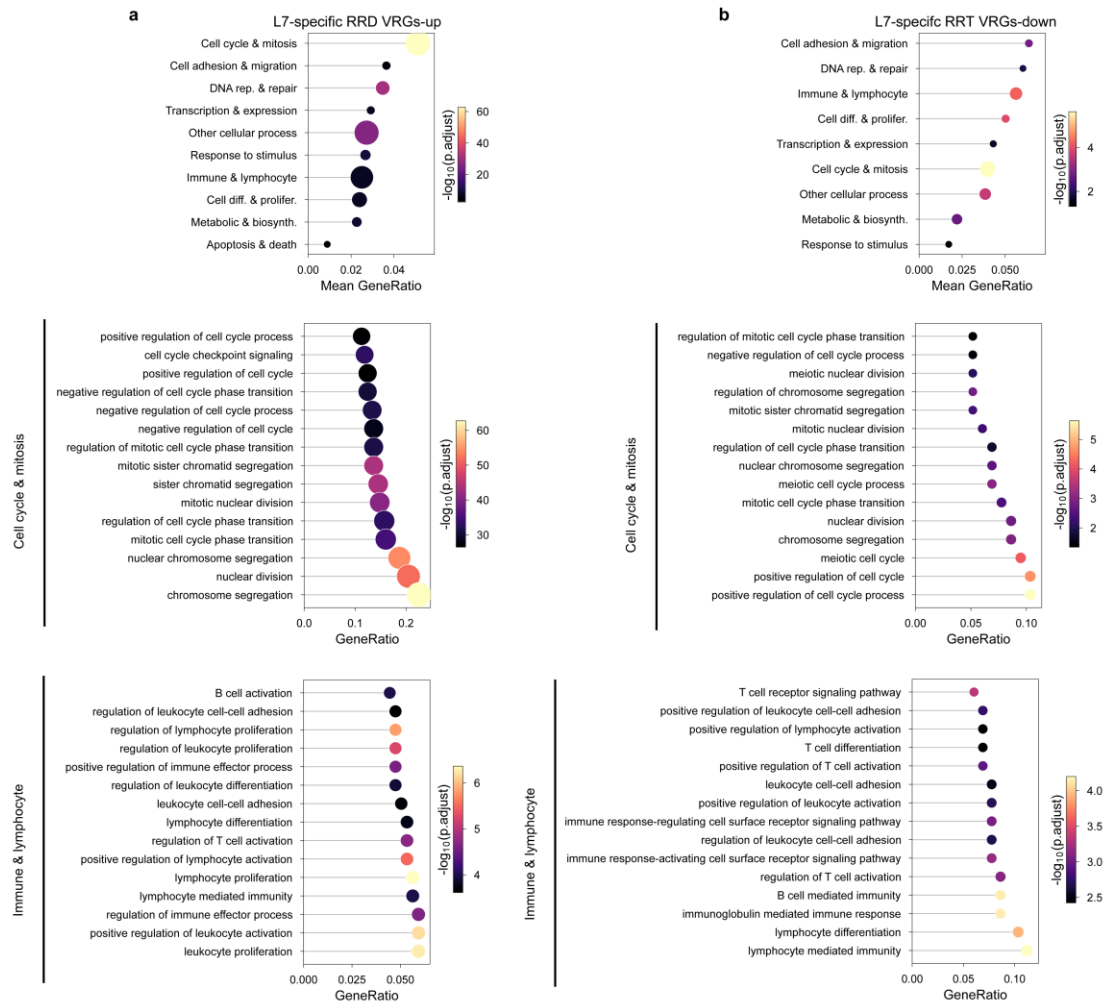


Figure S6 HD IAV infection induces impaired T-cell immunity. (a) GO enrichment analysis of LD-day7-specific RRT VRGs-up. **(b)** GO enrichment analysis of LD-day7-specific RRT VRGs-down.