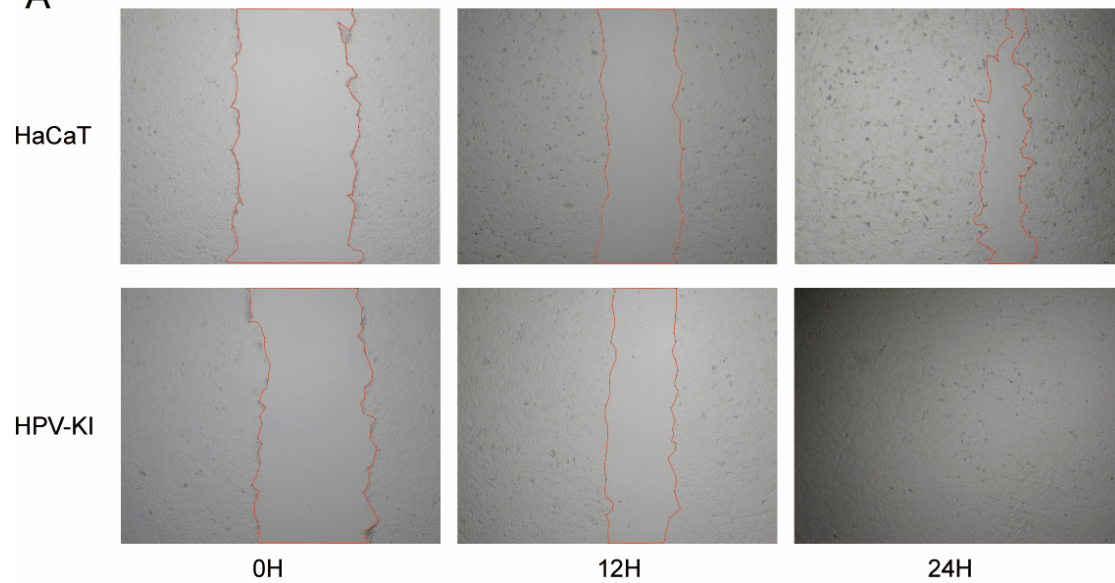


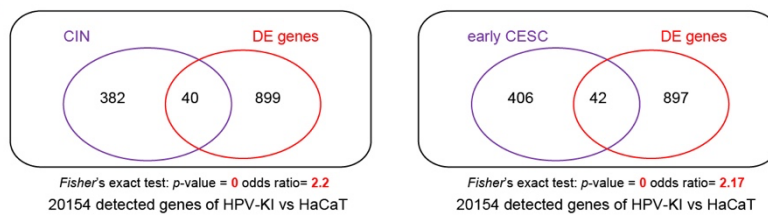
Supplementary Figures

A

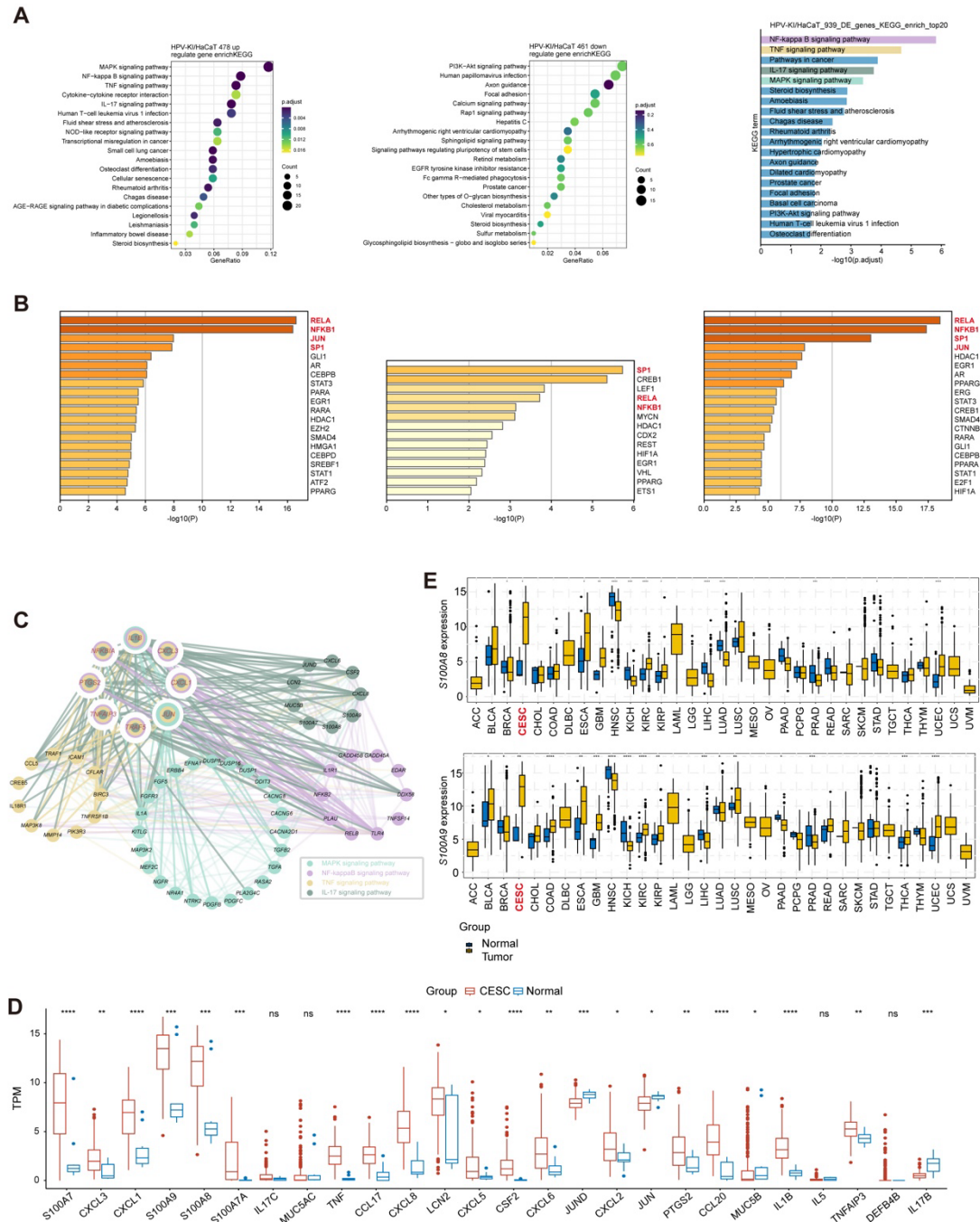


Supplementary Figure 1. (A) Wound healing assay of HaCaT and HPV-KI at 0h, 12h and 24h. wound healing rates are shown in **Fig. 1G**.

A

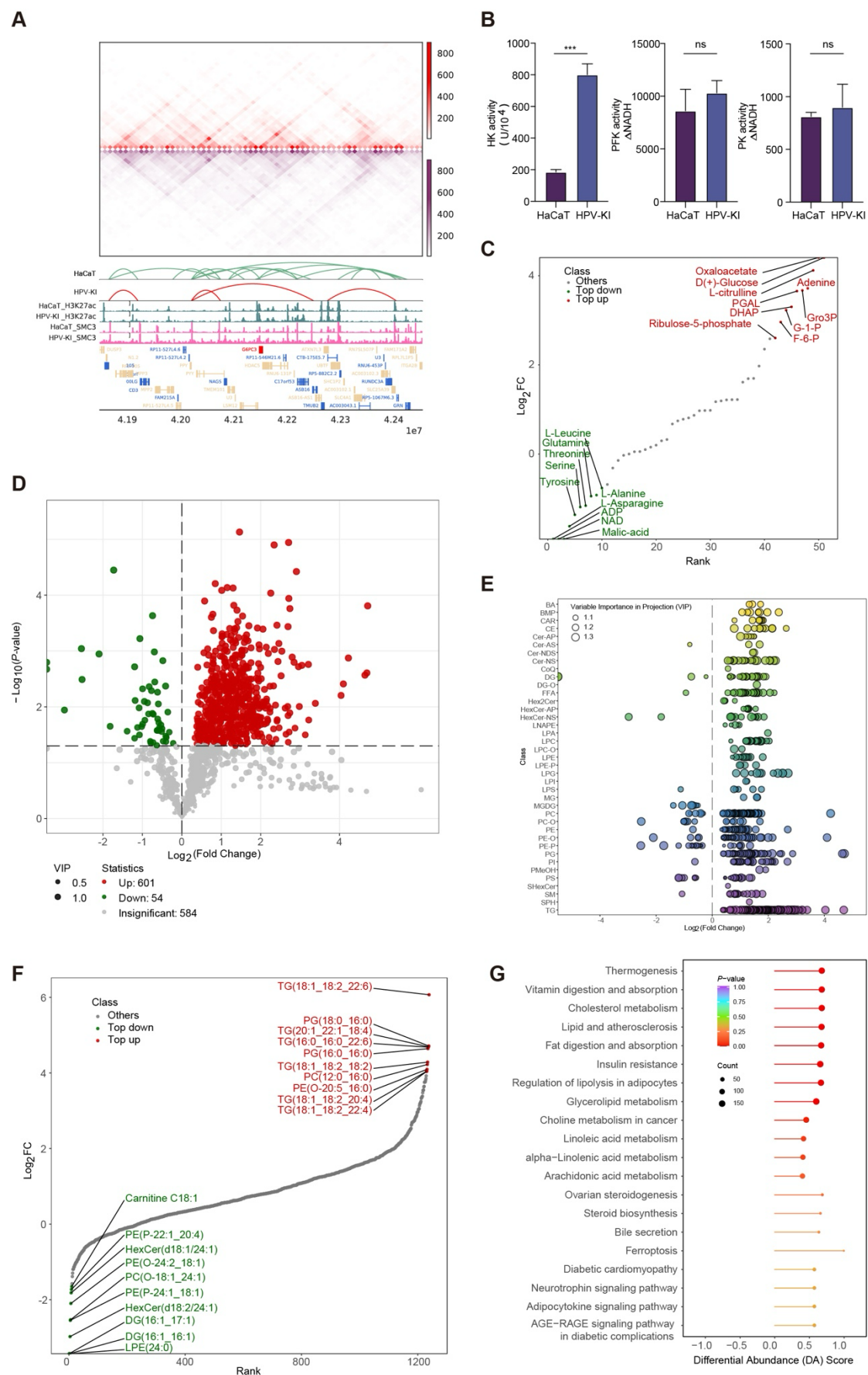


Supplementary Figure 2. (A) The left panel presents a *Fisher's* exact test comparing DE genes between HPV-KI and HaCaT with those from scRNA data of CIN compared to normal epithelial cells. The right panel illustrates the comparison of DE genes between HPV-KI and HaCaT with those of early-stage CESC compared to normal epithelial cells. the DE gene list is from Liu *et al.*, Sci. Adv. 9, eadd8977(2023).



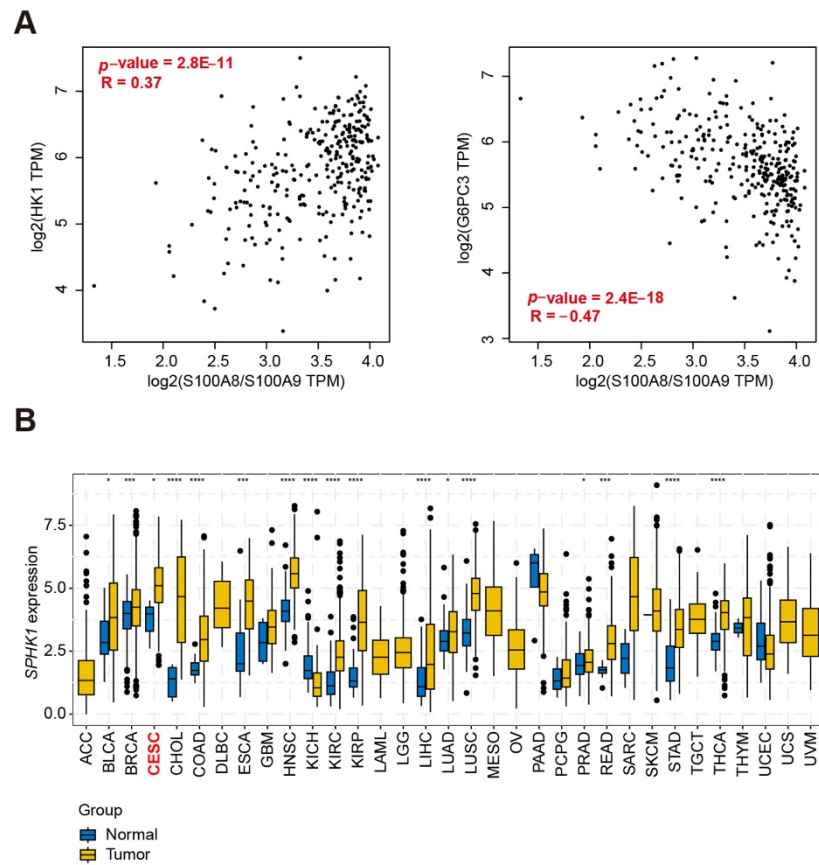
Supplementary Figure 3. (A) KEGG pathway enrichment analysis was performed for the up-regulated and down-regulated DE genes in HPV-KI/HaCaT cells. The top 20 enriched KEGG pathways were identified for 939 DEGs in HPV-KI/HaCaT cells. **(B)** The Metascape database was utilized to predict transcription factors associated with both the up-regulated and down-regulated DEGs, as well as the total set of 939 DEGs identified in HPV-KI/HaCaT cells. **(C)** A protein-protein interaction (PPI) network was constructed for important DEGs involved in the IL-17 signaling pathway, TNF signaling pathway, NF- κ B signaling pathway and MAPK signaling pathway. Genes shared by at least two pathways were considered as "Hub Genes".

(D) The expression of IL-17 pathway related genes between CSCE and normal was compared using data from the TCGA and GTEx database. **(E)** The expression levels of *S100A8* and *S100A9* were compared between different types of cancers and control samples. The Wilcoxon rank-sum test was applied to test statistical significance.

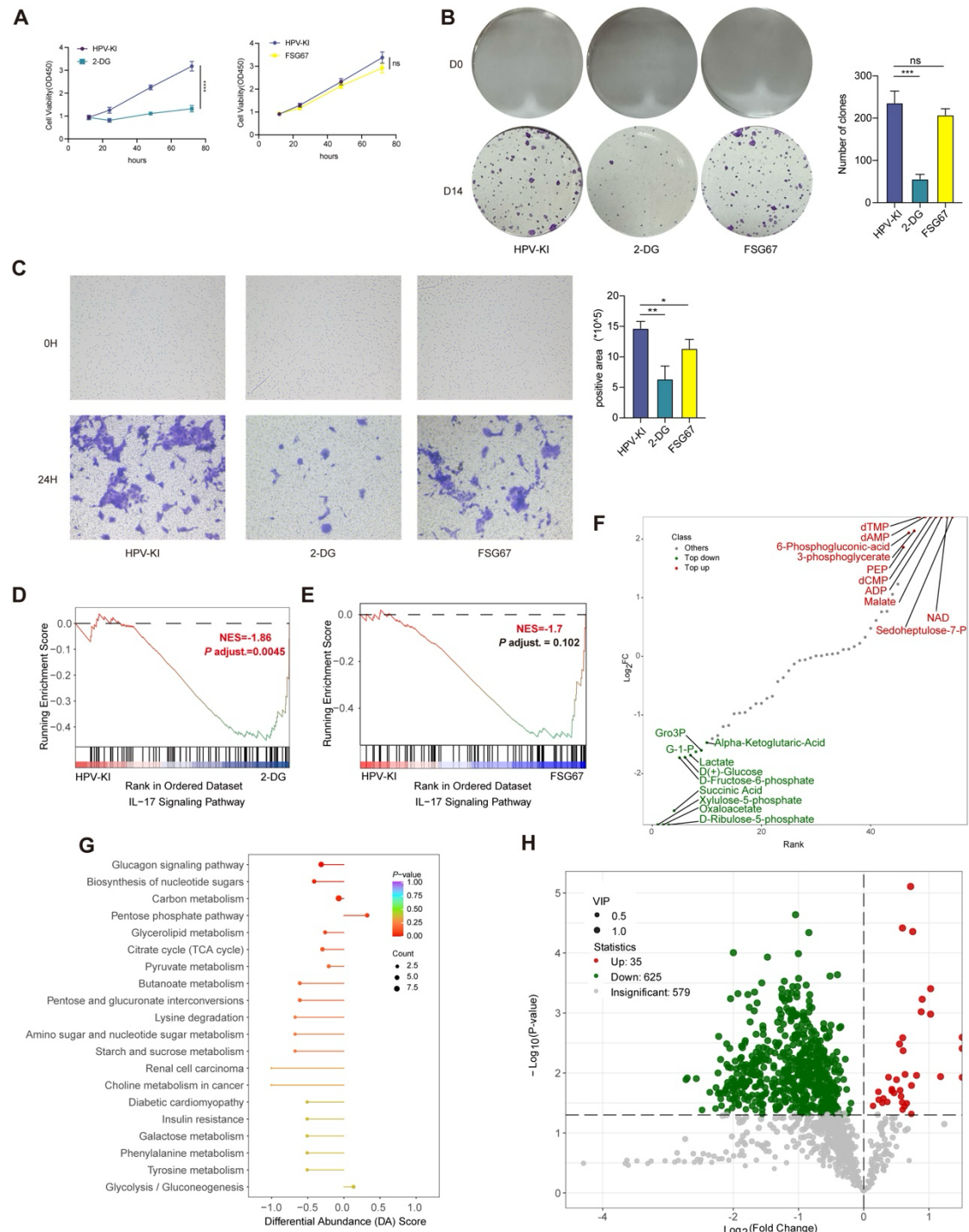


Supplementary Figure 4. (A) A Hi-C contact heatmap at the neighboring regions of *G6PC3*

(chr17: 42148097 - 42153712) along with corresponding tracks of the ChIP-seq profile were displayed. The gene track is shown in the bottom panel. **(B)** Bar plots illustrating the activity of HK, PFK, and PK in HPV-KI/HaCaT cells related to Fig. 4D. The data were calculated by two-tailed Student's *t*-test. *P* value was denoted as ****P* < 0.001 and “ns” represented “not significant”. **(C)** Dynamic distribution map of Fold change (FC) ranking of the difference in metabolite of carbon metabolism from HaCaT/HPV-KI. Top 10 metabolites down (green) and up (red) were marked. **(D)** Volcano plots were used to visualize the differences in the abundance levels of lipid metabolites in HaCaT/HPV-KI, with red spots indicating up-regulated differential metabolites, green spots indicating down-regulated differential metabolites, and grey spots indicating detected metabolites that did not show significant differences at *p* < 0.05. **(E)** Scatter plots were employed to illustrate the abundance differences of lipids from different subclasses in HaCaT/HPV-KI, with the abscissa representing the log₂ FC between the two groups and the size of each dot representing its variable importance in projection (VIP) value. **(F)** Dynamic distribution map of FC ranking of the difference in metabolite in lipid-omics from HaCaT/HPV-KI. Top10 metabolites down (green) and up (red) were marked. **(G)** KEGG analysis reveals Lipid-omics changes between HPV-KI and HaCaT based on the DA Score of the pathway.

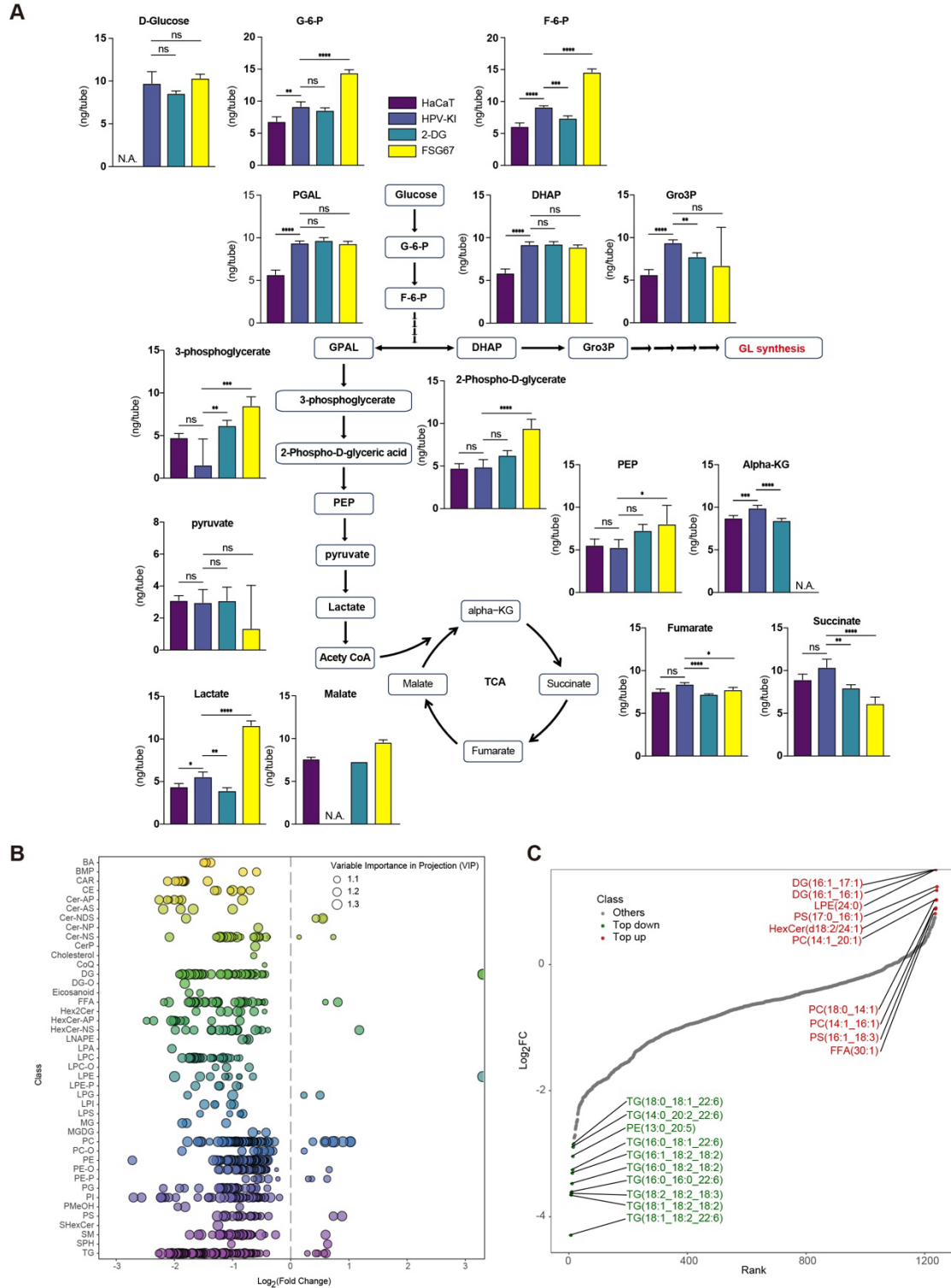


Supplementary Figure 5. (A) Correlation analysis of *S100A8/A9* with *HK1* and *G6PC3* in the TCGA database was conducted, and statistical analysis was performed using *Pearson's* correlation test. **(B)** Expression levels of *SPHK1* between different types of cancer and control respectively. The Wilcoxon rank-sum test was employed to access statistical significance.



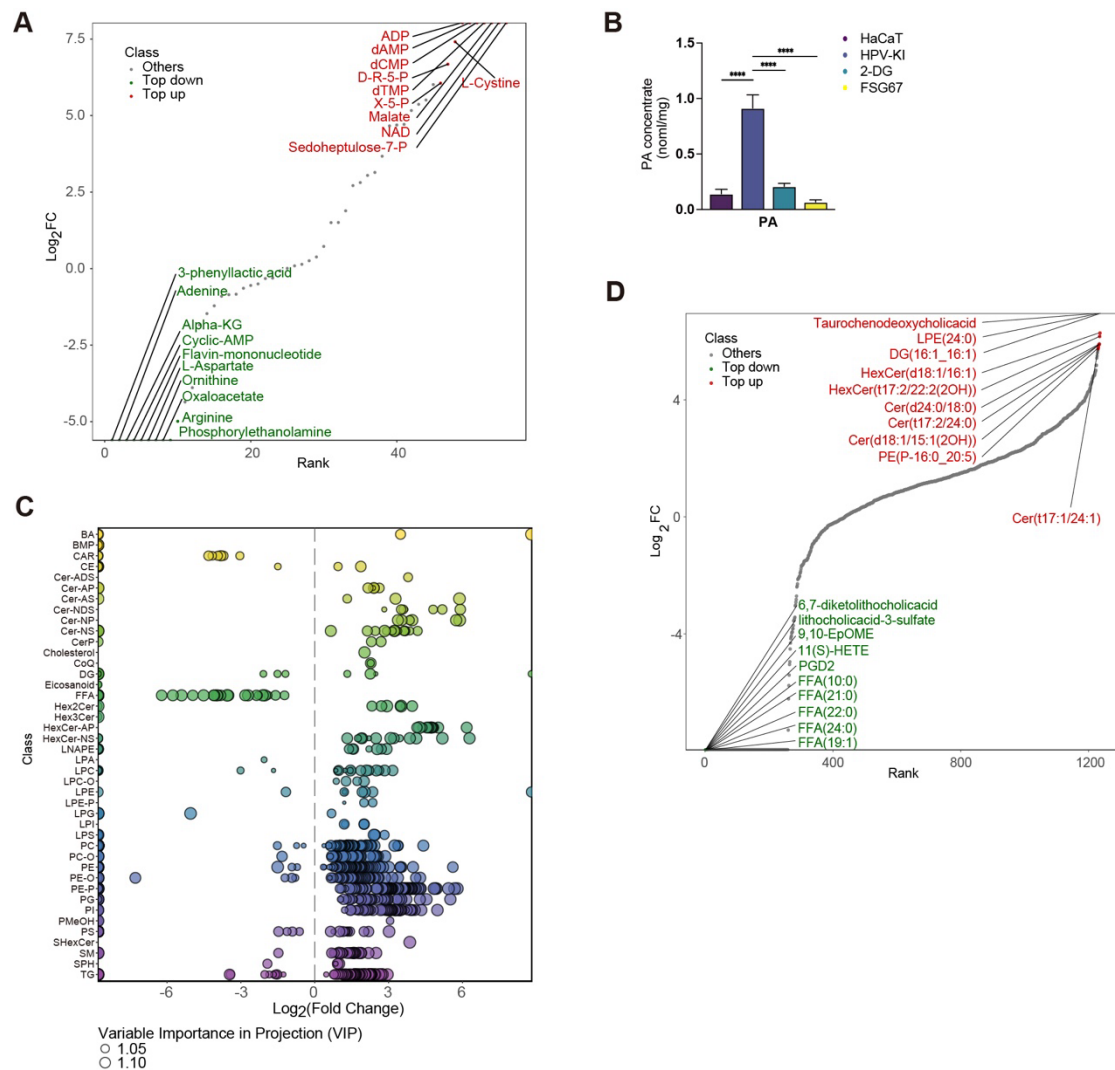
Supplementary Figure 6. (A) HPV-KI cell viability treated by 2-DG (2mmol) and FSG67 (20μmol) was detected by CCK-8. (B) Clone formation assay of HPV-KI, 2-DG- HPV-KI and FSG67- treated HPV-KI. (C) Transwell showing invasiveness of HPV-KI, 2-DG- treated HPV-KI and FSG67- treated HPV-KI. (D) GSEA analysis for IL-17 signaling pathway in 2-DG-treated HPV-KI/HPV-KI cells. (E) GSEA analysis was performed to investigate the IL-17 signaling pathway in FSG67- treated HPV-KI/HPV-KI cells. (F) Dynamic distribution map of

FC ranking of the difference in metabolites in carbon metabolism from 2-DG- treated HPV-KI /HPV-KI. Top10 metabolites down (green) and up (red) were marked. **(G)** KEGG analysis changes between 2-DG- treated HPV-KI and HPV-KI based on DA score in carbon metabolism. **(H)** Volcano plot showing the differences in the levels of lipid metabolites in 2-DG- treated HPV-KI /HPV-KI, with red spots indicating up-regulated differential metabolites, green spots indicating down-regulated differential metabolites, and grey spots indicating detected metabolites that did not show significant differences at $p < 0.05$.

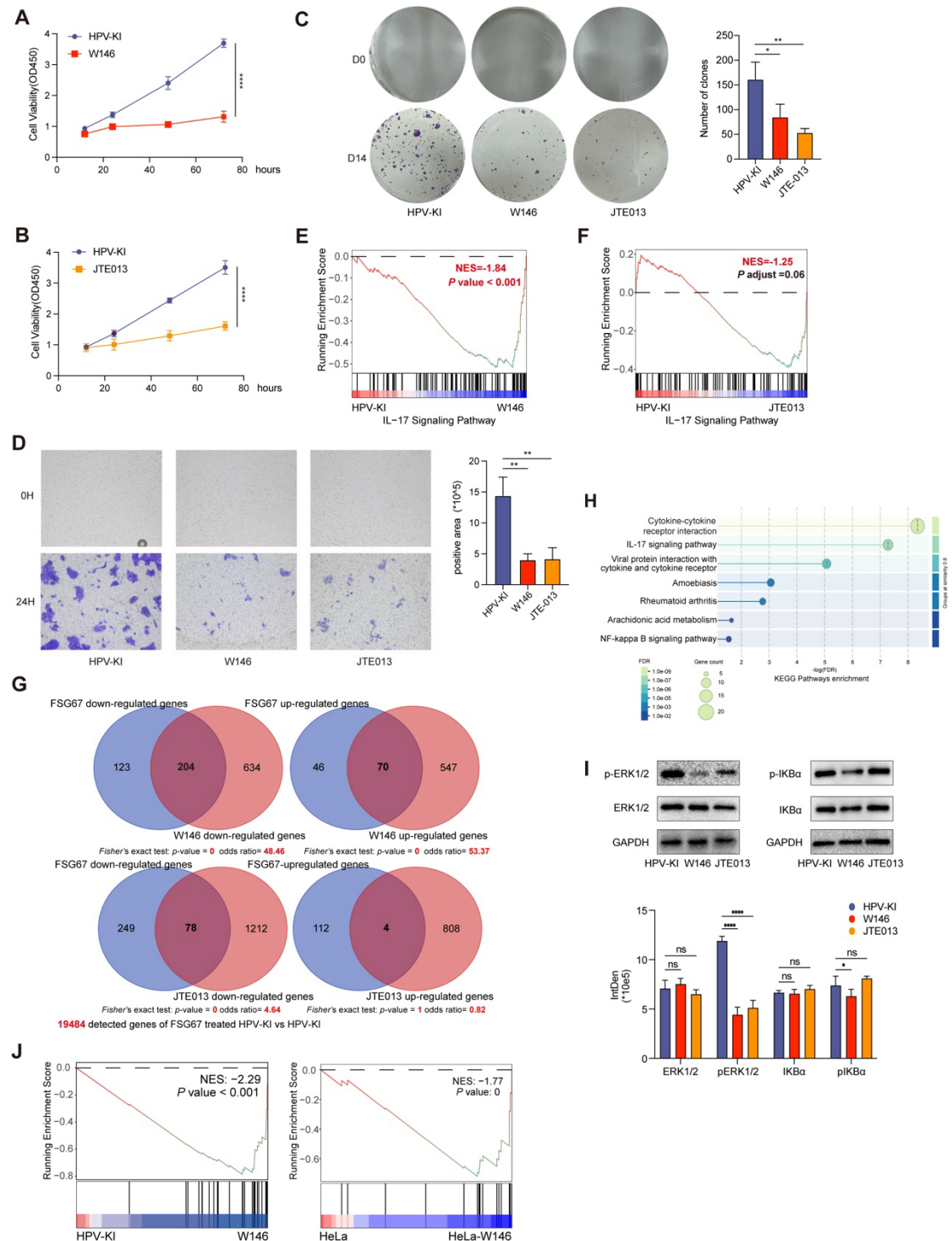


Supplementary Figure 7. (A) The abundance of metabolites in glycolysis and TCA cycle was compared among HaCaT, HPV-KI, 2-DG- treated HPV-KI and FSG67- treated HPV-KI using bar plots to display log_2 FC values (one-way ANOVA-test, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ and $****P < 0.0001$, “ns” represented “not significant”, n/a indicates “not available”). **(B)** Scatter plot showing the abundance differences of lipids from different subclass in 2-DG-

treated HPV-KI /HPV-KI. (C) Dynamic distribution map of FC Ranking of the difference in metabolite in lipid-omics from 2-DG- treated HPV-KI /HPV-KI. Top10 metabolites down (green) and up (red) were marked.

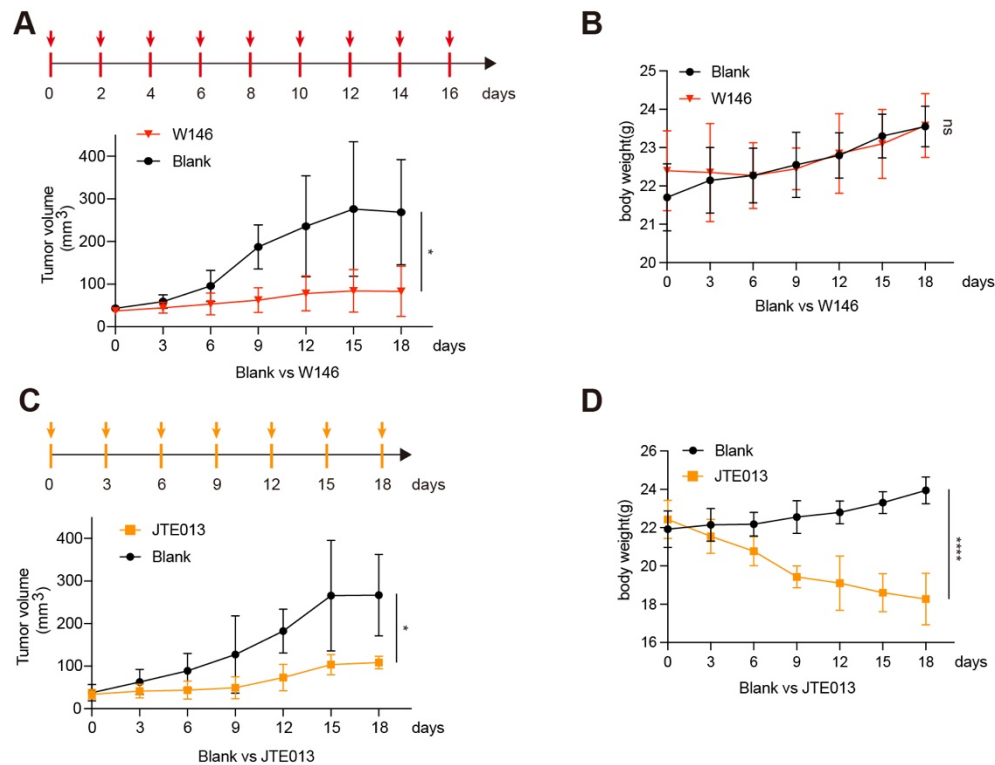


Supplementary Figure 8. (A) Dynamic distribution map of FC Ranking of the difference in metabolite in carbon metabolism from FSG67- treated HPV-KI /HPV-KI. Top10 metabolites down (green) and up (red) were marked. (B) The abundance of PA concentrate in HaCaT, HPV-KI, 2-DG- treated HPV-KI, and FSG67- treated HPV-KI is shown. (C) Scatter plot showing the abundance differences of lipids from different subclass in FSG67- treated HPV-KI /HPV-KI. (D) Dynamic distribution map of FC ranking of the difference in metabolite in lipid-omics from FSG67- treated HPV-KI/HPV-KI. Top10 metabolites down (green) and up (red) were marked.



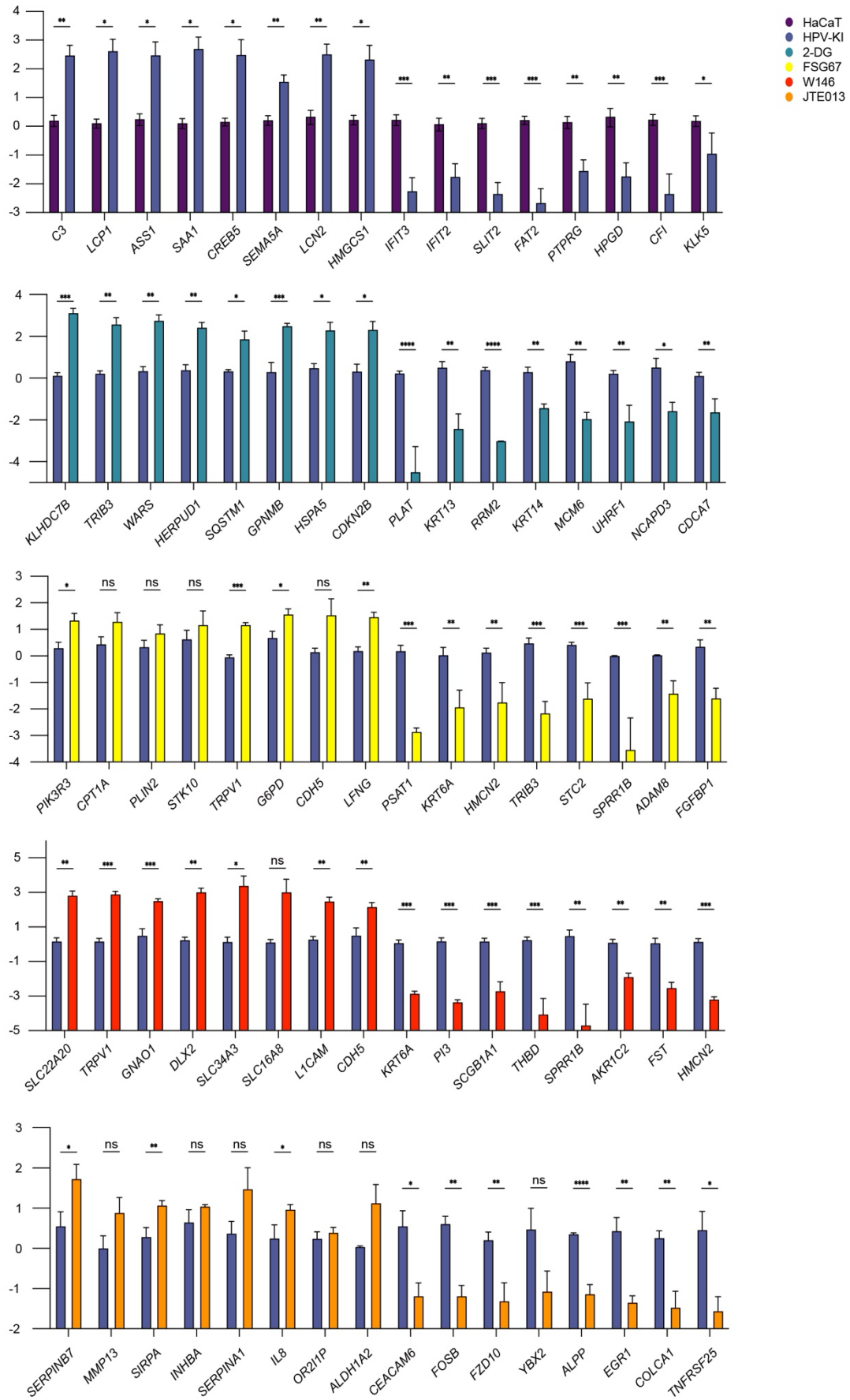
Supplementary Figure 9. (A) Cell viability of W146-treated and (B) JTE013-treated HPV-KI and untreated HPV-KI at 12 h, 24 h, 48h and 72 h has determined by CCK-8 assay. (C) Clone formation assay of HPV-KI, W146- treated HPV-KI and JTE013- treated HPV-KI. (D) Transwell showing invasiveness of HPV-KI, W146- treated HPV-KI and JTE013- treated HPV-KI. (E) GSEA analysis for IL-17 pathway in W146- treated HPV-KI/HPV-KI cells. (F) GSEA analysis for IL-17 pathway in JTE013- treated HPV-KI /HPV-KI cells. (G) Venn diagram

illustrating the up-regulation and down-regulation of genes between FSG67- and W146-, FSG67- and JTE013- treated HPV-KI. **(H)** KEGG enrichment for genes synchronically down-regulated in FSG67- and W146- treated HPV-KI. **(I)** ERK1/2, I κ B α , phosphorylated ERK1/2, and phosphorylated I κ B α protein levels in HPV-KI, W146- treated HPV-KI and JTE013- treated HPV-KI. The data were calculated by two-tailed Student's *t*-test. *P* value was denoted as **P* < 0.05, ***P* < 0.01, and ****P* < 0.001, *****P* < 0.0001, “ns” represented “not significant”.



Supplementary Figure 10. (A) Tumor volumes of PDX tumors treated with PBS or W146, calculated using the formula $0.52 \times \text{length (L)} \times \text{width (W)}^2$. The arrow indicates the time of drug administration. (B) Body weight changes of PBS and W146- treated NOD/SCID mice. (C) Measurement of tumor volumes in PDX models following treatment with DMSO/TWEEN-20/PEG or JTE013. The arrow indicates the time of drug administration. (D) Body weight changes of DMSO/TWEEN-20/PEG and JTE013- treated NOD/SCID mice.

A



Supplementary Figure 11. (A) Validation of the top DEGs across experimental groups was conducted by qPCR, with $\log_2$ FC values calculated to quantify gene expression alterations. The primer sequences used for qPCR analysis are provided in Supplementary Table 1. The data were calculated by two-tailed Student's *t*-test. *P* value was denoted as $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$, $****P < 0.0001$, “ns” represented “not significant”.