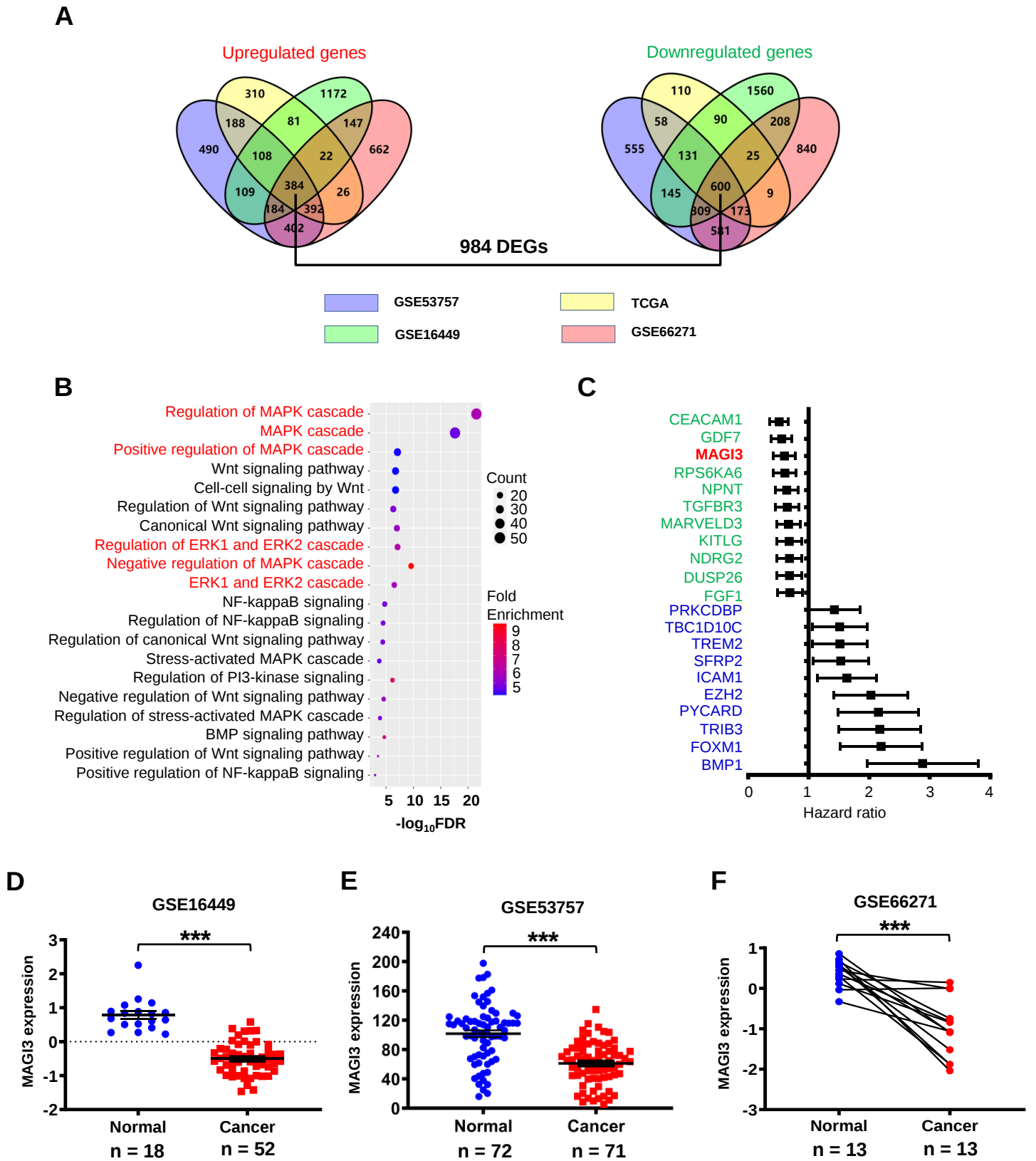
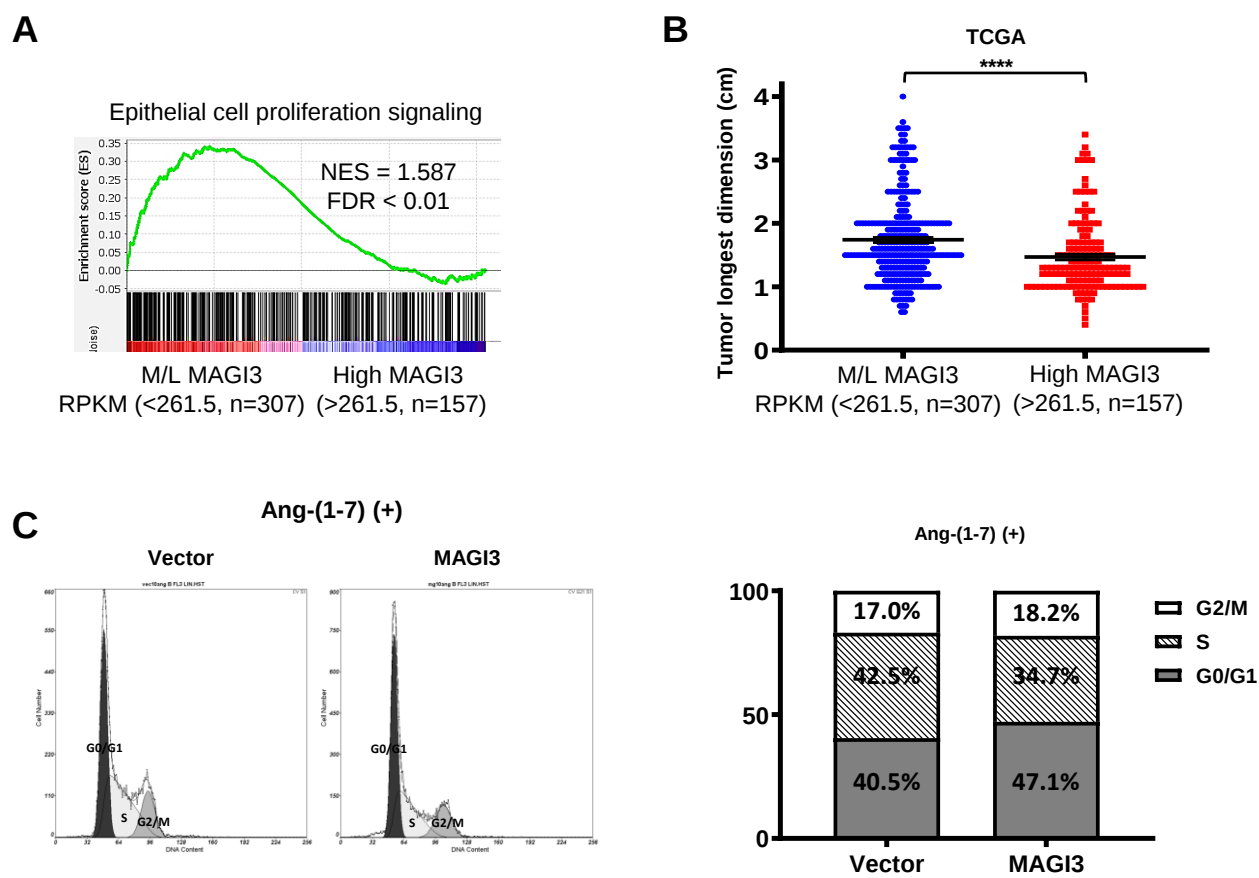


Supplementary Figure 1



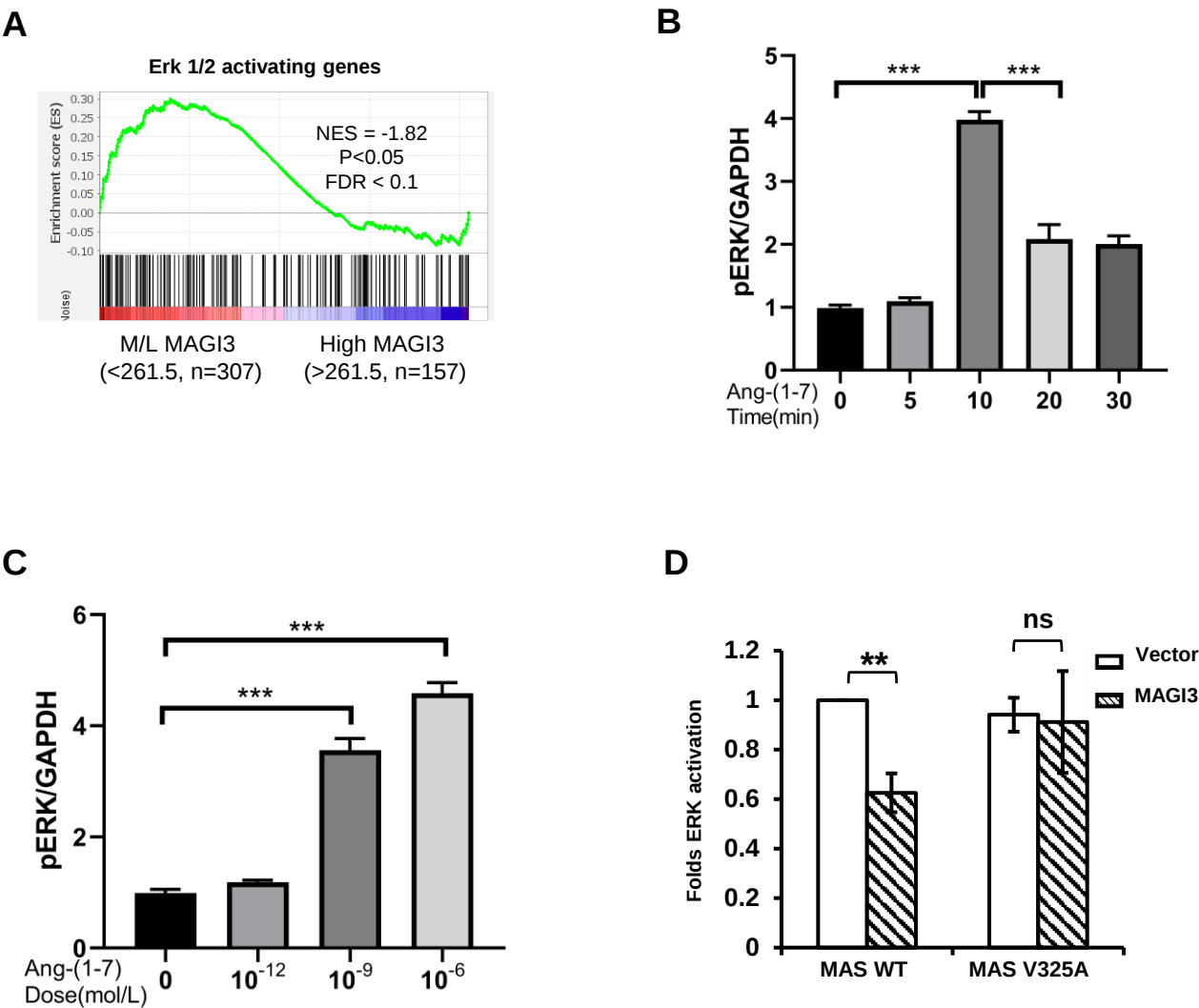
**Suppl. Figure 1. MAGI3 emerges as a novel prognostic marker in ccRCC and participates in MAPK signaling.**  
**A.** Venn diagram illustrating common DEGs identified in four independent ccRCC cohorts through mRNA expression profiling of tumor and normal renal tissue.  
**B.** KEGG pathway enrichment analysis of the DEGs using the DAVID bioinformatics database.  
**C.** Hazard ration of MAPK-related genes based on mRNA expression in ccRCC patients from TCGA analyzed for overall survival (OS).  
**D, E.** Comparison of MAGI3 mRNA expression levels in ccRCC specimens to normal tissues from GSE16449 (D) and GSE53757 (E).  
**F.** Evaluation of MAGI3 mRNA expression levels in ccRCC specimens compared to paired normal tissues from GSE66271.  
Data presented as mean  $\pm$  SEM, with statistical significance calculated using the paired t-test. \*\*\*,  $P < 0.001$ .

Supplementary Figure 2



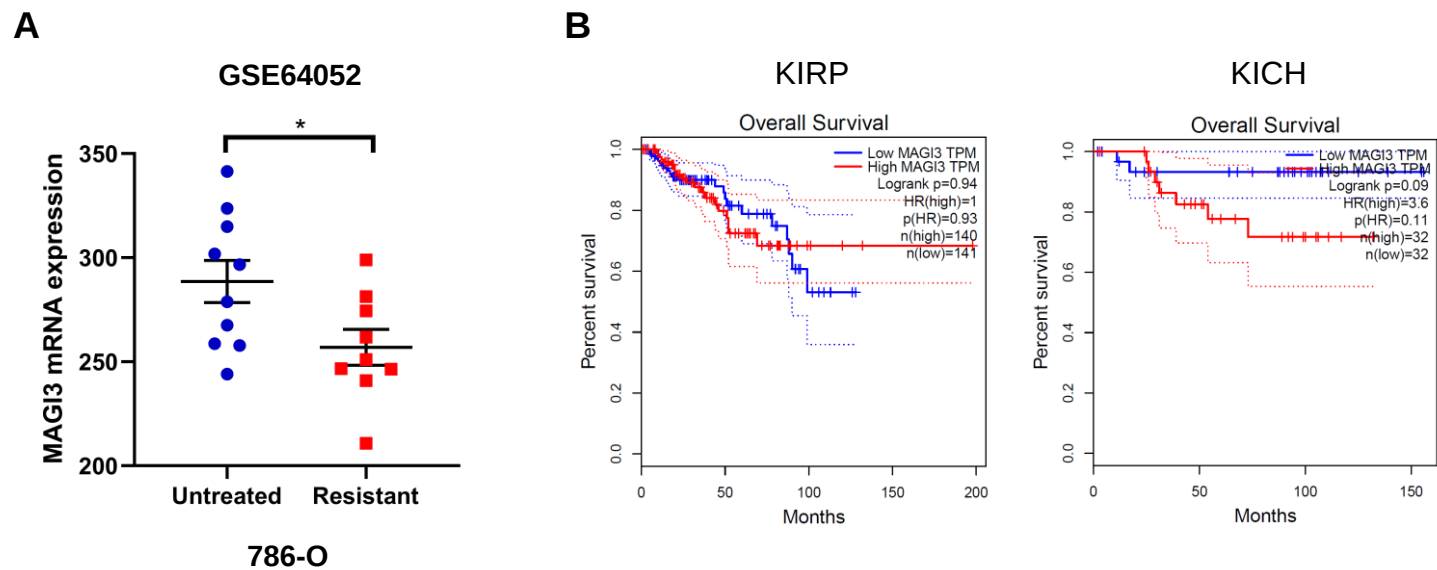
**Suppl. Figure 2. The significant association of MAGI3 with tumor proliferation in ccRCC.**  
**A.** GSEA enrichment plots exhibit significant activation of epithelial cell proliferation pathways in ccRCC specimens with middle-low (M/L) MAGI3 expression from the TCGA ccRCC dataset.  
**B.** Tumor lengths were notably different between TCGA ccRCC patients with M/L and high MAGI3 expression, assessed through t-test analysis (\*\*\*\*,  $P < 0.0001$ ).  
**C.** MAGI3 overexpression induces cell cycle arrest. Cell cycle arrest at the G1-S transition in 786-O cells is illustrated by flow cytometry assay following MAGI3 overexpression.

Supplementary Figure 3



**Suppl. Figure 3. MAGI3 inhibits the activation of the ERK pathway through its interaction with MAS.**  
**A.** GSEA enrichment plots reveal significant activation of ERK pathways in ccRCC specimens with middle-low (M/L) MAGI3 expression from the TCGA ccRCC dataset.  
**B.** Quantification of pERK/GAPDH in Figure 4A.  
**C.** Quantification of pERK/GAPDH in Figure 4B.  
**D.** Overexpression of MAGI3 reduced phospho-ERK levels in cells transfected with the MAS WT but not the MAS V325A mutant. Data is presented as mean  $\pm$  SEM, with statistical significance determined using an unpaired t-test. \*\* indicates significance at  $P < 0.01$ ; NS indicates non-significance.

Supplementary Figure 4



Suppl. Figure 4. MAGI3 is downregulated in Sunitinib-resistant renal clear cell carcinoma cell lines, and has no prognostic significance for other subtypes of renal cancer patients.

A. Significant downregulation of MAGI3 mRNA in sunitinib-resistant ccRCC 786-O cell line (GSE64052). Mean  $\pm$  SEM. Two-tailed unpaired t-test. \*\*\*p < 0.001.

B. KM survival plots for overall survival (OS) based on MAGI3 mRNA expression in kidney renal papillary cell carcinoma (KIRP) and Kidney Chromophobe (KICH) patients from TCGA dataset (p > 0.05, log-rank test).