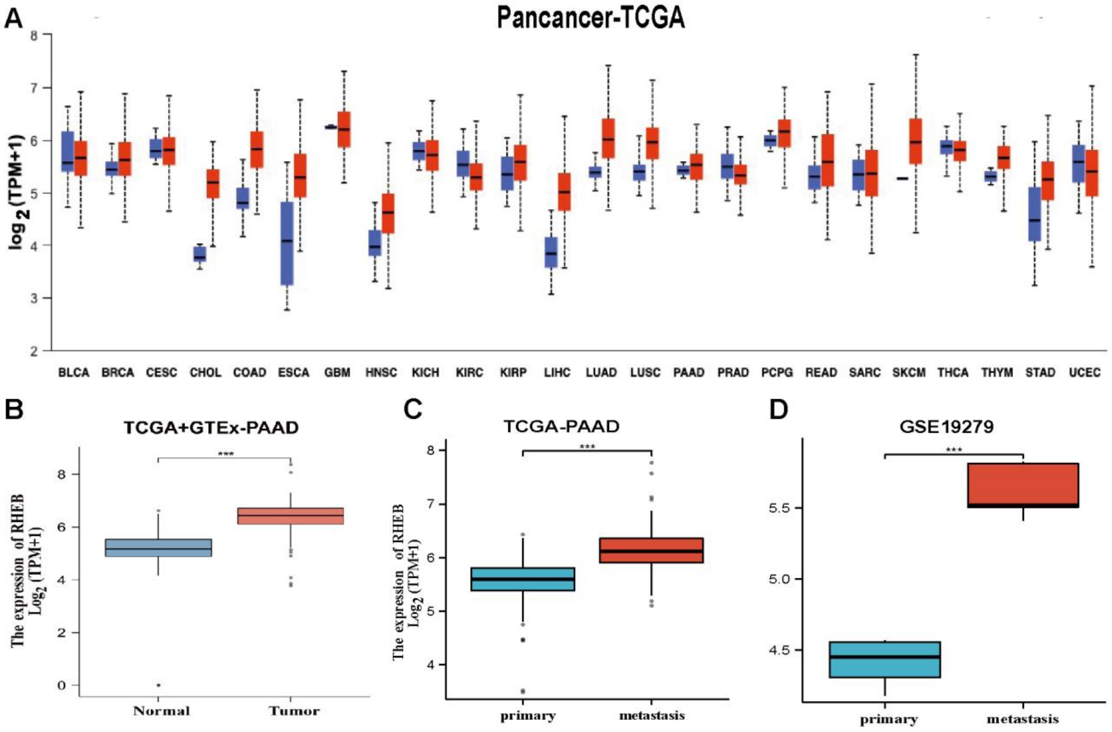
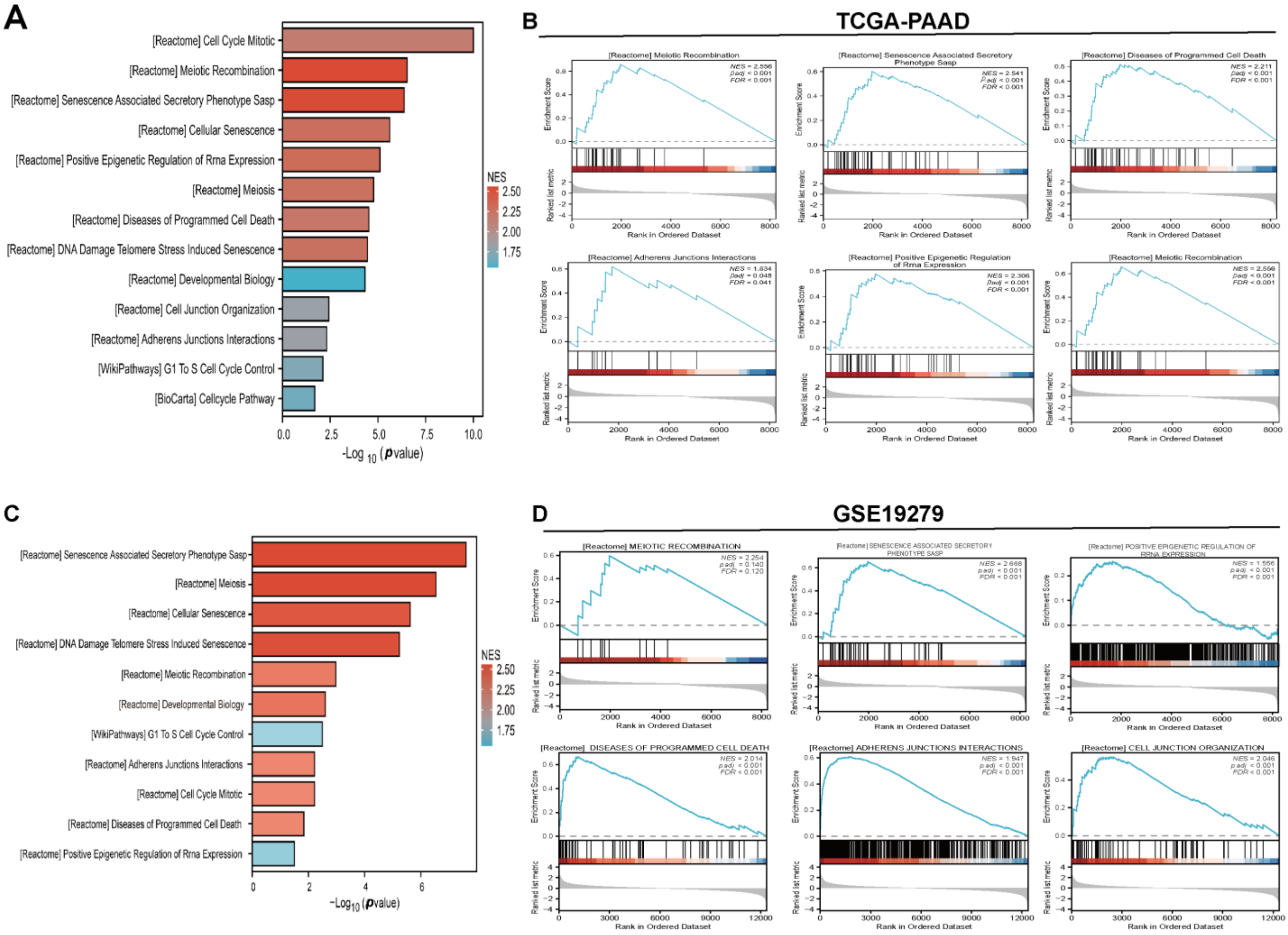
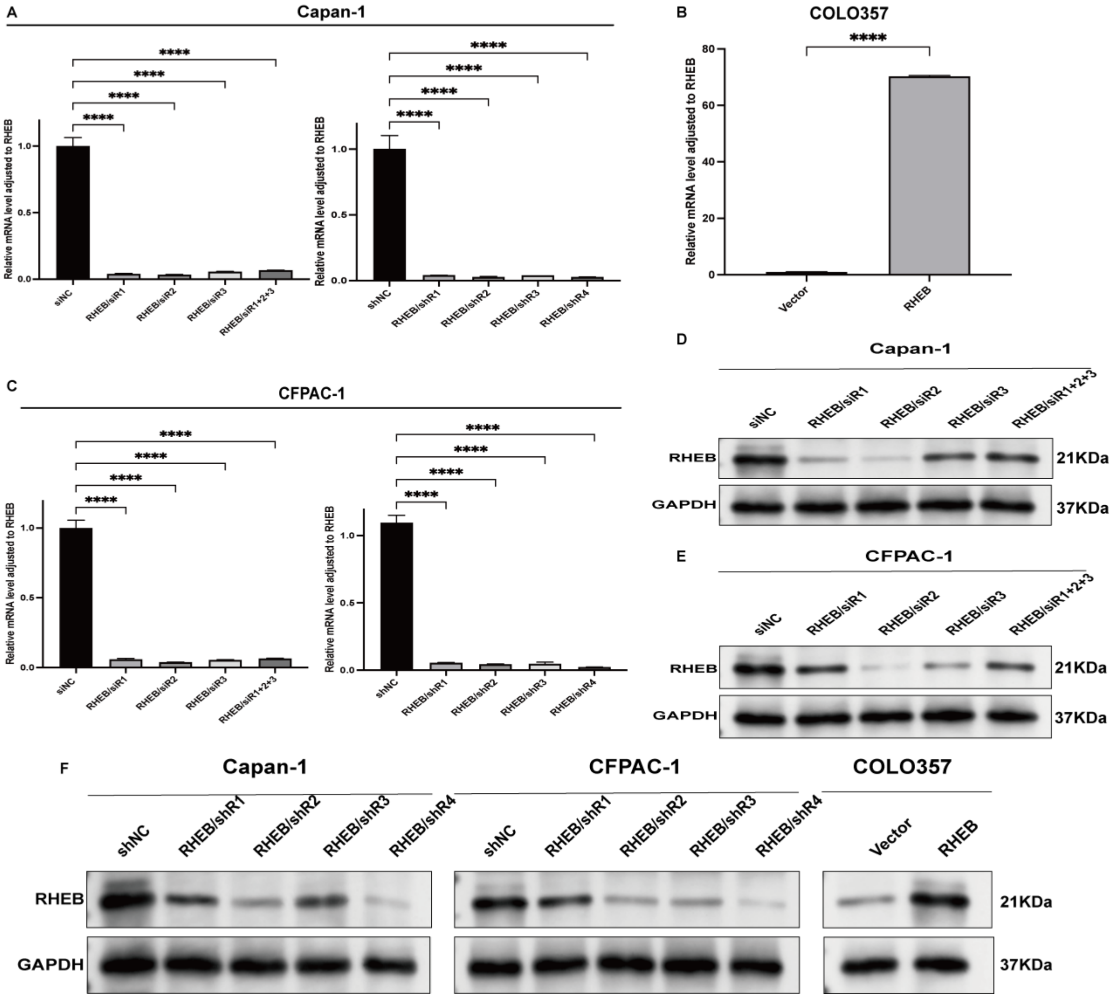


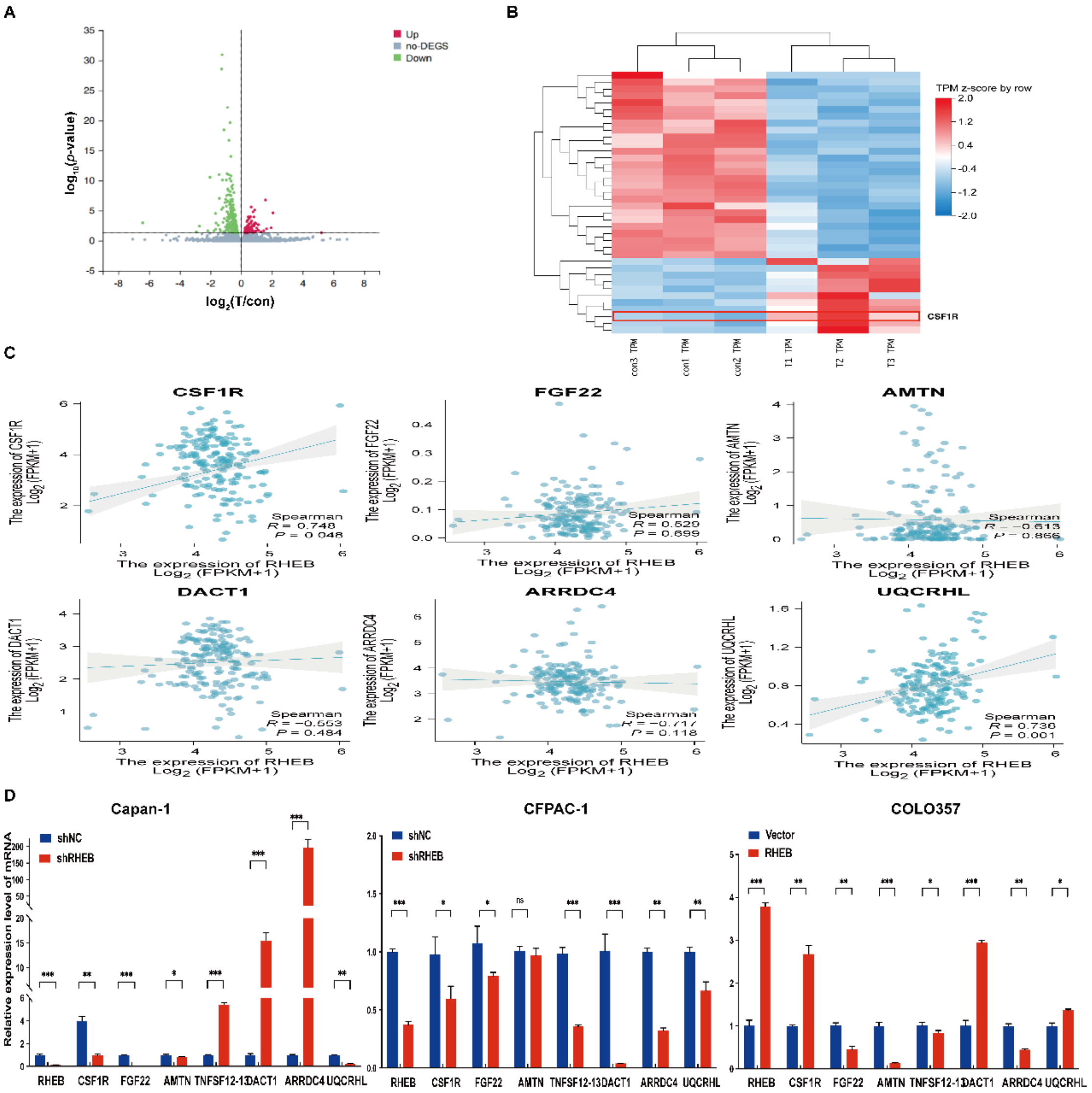
Supplementary Figure 1 Expression levels of RHEB in pan-cancer and PAAD. A: Expression levels of RHEB in tumor and normal tissues across 24 tumor types; B: Expression levels of RHEB in TGCA-PAAD and GTEx-PAAD; C, D: Expression levels of RHEB in primary and metastasis tissues of TGCA-PAAD and GSE19279 (***p-value $<$ 0.001). Note: RHEB, Ras homolog enriched in brain; PAAD, pancreatic adenocarcinoma; TCGA, the Cancer Genome Atlas. (Blue represents normal tissue, while red represents tumor tissue.)



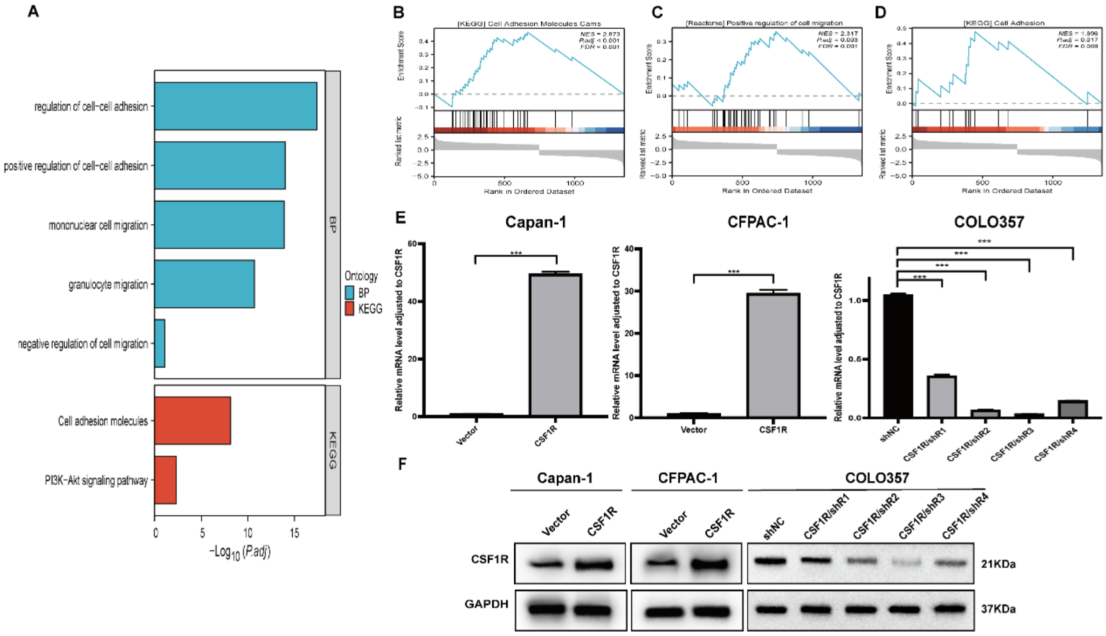
Supplementary Figure 2 Functional enrichment analyses of RHEB. A: GO and KEGG of RHEB in TCGA-PAAD; B: GSEA of RHEB in TCGA-PAAD; C: GO and KEGG of RHEB in GSE19279GSEA of RHEB in TCGA-PAAD; D: GSEA of RHEB in GSE19279. Note: RHEB, Ras homolog enriched in brain; PAAD, pancreatic adenocarcinoma; TCGA, the Cancer Genome Atlas; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; GSEA, Gene set enrichment analysis.



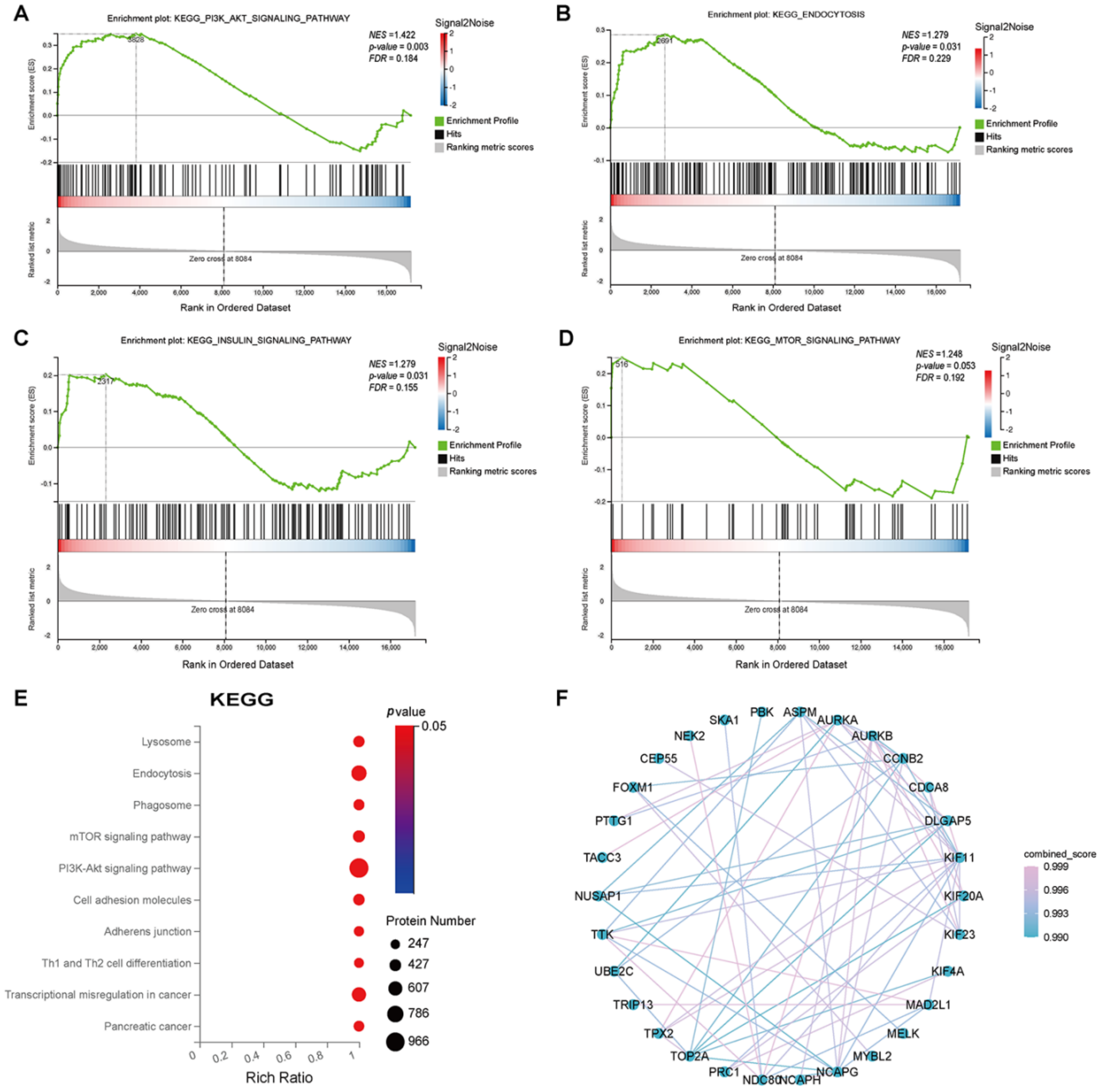
Supplementary Figure 3 Construction of RHEB transfected cell lines. A, B, C: The expression of RHEB was confirmed by RT-qPCR analyses in the Capan-1 and CFPAC-1 cells transfected with the control siRNA/shRNA or the RHEB silencing by siRNA/shRNA, in COLO357 cells transfected with the control vector or the RHEB overexpression vector; D, E, F: The expression of RHEB was confirmed by Western blot analyses in the Capan-1 and CFPAC-1 cells transfected with the control siRNA/shRNA or the RHEB silencing by siRNA/shRNA, in COLO357 cells transfected with the control vector or the RHEB overexpression vector (*****p*-value < 0.0001). Note: RHEB, Ras homolog enriched in brain.



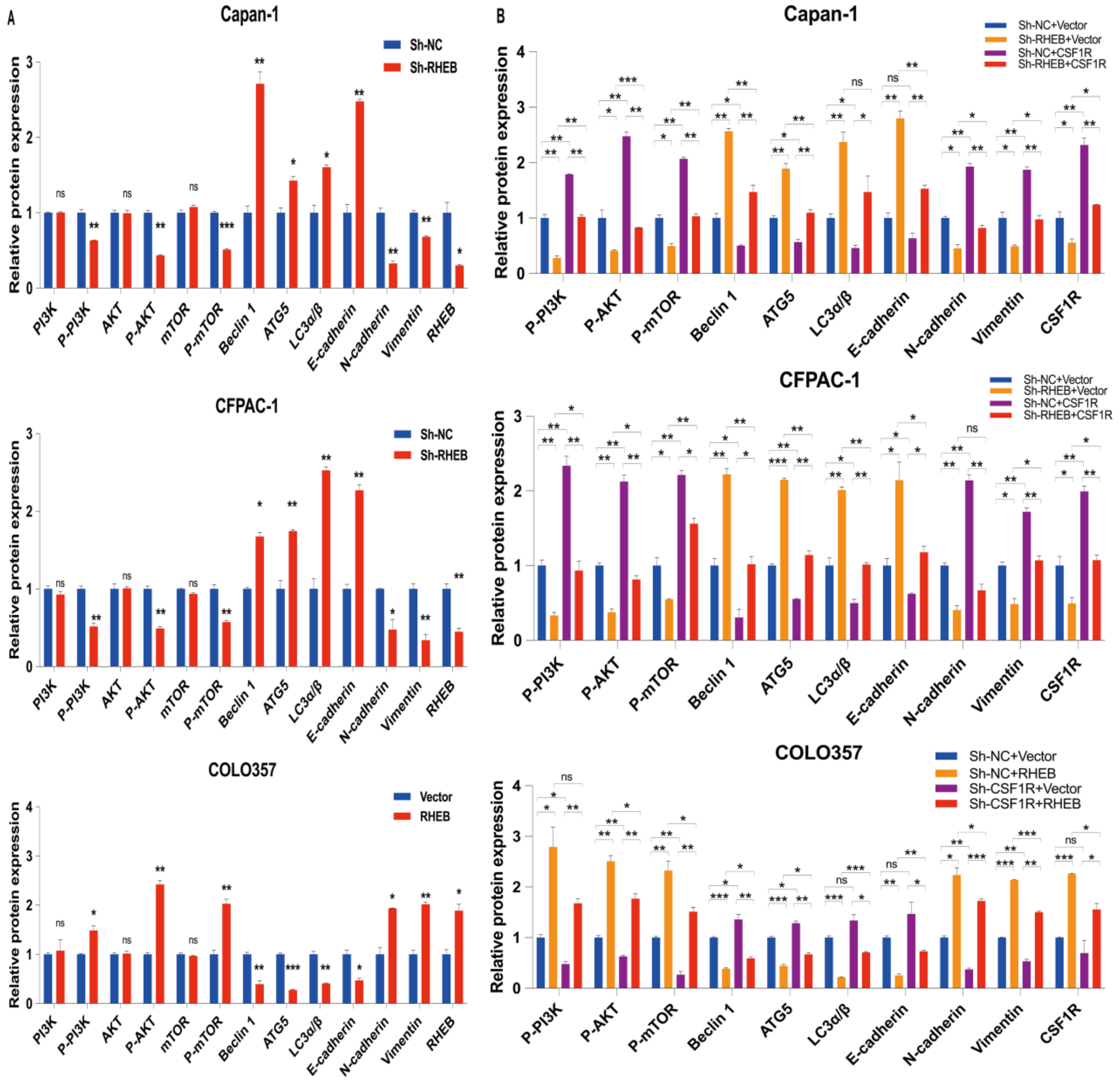
Supplementary Figure 4 Validation of differential genes between Capan-1 stably transfected shRHEB and its control cell lines. A, B: RNA high-throughput sequencing screens differential expression genes (DEGs) in Capan-1 cells stably expressing the control shNC and shRHEB; C: The correlation analyses between DEGs and RHEB; D: The expression of RHEB and DEGs was confirmed by RT-qPCR analyses in the Capan-1 and CFPAC-1 cells transfected with the shRNA or the shRHEB, in COLO357 cells transfected with the vector or the RHEB (**p*-value < 0.05, ***p*-value < 0.01, ****p*-value < 0.001, ns>0.05). Note: RHEB, Ras homolog enriched in brain.



Supplementary Figure 5 Functional enrichment analyses of CSF1R. A: GO and KEGG of CSF1R; B, C, D: GSEA of CSF1R; E: The expression of CSF1R was confirmed by RT-qPCR analyses in the Capan-1 and CFPAC-1 cells transfected with the control vector or the CSF1R overexpression vector, in COLO357 cells transfected with the control shRNA or the CSF1R silencing by shRNA; F: The expression of CSF1R was confirmed by Western blot analyses in the Capan-1 and CFPAC-1 cells transfected with the control vector or the CSF1R overexpression vector, in COLO357 cells transfected with the control shRNA or the CSF1R silencing by shRNA (****p*-value $<$ 0.001). Note: GSEA, Gene set enrichment analysis; CSF1R, Ras homolog enriched in brain.



Supplementary Figure 6 Functional enrichment analyses of DEGs. A, B, C, D: GSEA of differential genes between Capan-1 stably-transfected shRHEB and its control cell lines; E: KEGG of differential genes between Capan-1 stably-transfected shRHEB and its control cell lines; F: Protein-Protein Interaction (PPI) network analysis of RHEB. Note: RHEB, Ras homolog enriched in brain; KEGG, Kyoto Encyclopedia of Genes and Genomes.



Supplementary Figure 7 Western Blot quantitative analysis A: Western blot quantitative analyses of the PI3K/AKT/mTOR signaling pathway biomarkers, PI3K, p-PI3K, AKT, p-AKT, mTOR, and p-mTOR; the autophagy biomarkers, Beclin 1, ATG5 and LC3; and the epithelial-mesenchymal transformation (EMT) biomarkers, E-cadherin, N-cadherin and Vimentin, and RHEB; B: quantitative analyses of p-PI3K, p-AKT, and p-mTOR, and the autophagy biomarkers, Beclin 1, ATG5 and LC3, and the EMT biomarkers, E-cadherin, N-cadherin and Vimentin in the Capan-1 and CFPAC-1 cells stably expressing the siNC and the siRHEB were transfected transiently with the vector or the CSF1R, COLO357 cells stably expressing Vector and RHEB transfected with shNC and shCSF1R (*p-value < 0.05, **p-value < 0.01, ***p-value < 0.001, ns>0.05). Note: RHEB, Ras homolog enriched in brain; mTOR, Mammalian target of rapamycin; PC, Pancreatic cancer. p-PI3K corresponds to the Tyr524 phosphorylation site of PI3K; p-AKT corresponds to the Ser473 phosphorylation site of AKT

Supplementary Table 1 Comparison of clinicopathological features between the high expression- and low expression-RHEB subgroups in the TCGA-PAAD

Characteristics	Low expression of RHEB	High expression of RHEB	*P* value
n	89	90	
Age, n (%)			0.0867
<= 65	41 (22.9%)	53 (29.6%)	
> 65	48 (26.8%)	37 (20.7%)	
Gender, n (%)			0.713
Female	41 (22.9%)	39 (21.8%)	
Male	48 (26.8%)	51 (28.5%)	
Pathologic T stage, n (%)			0.0088
T1&T2	74 (41.8%)	15 (8.5%)	
T3&T4	16 (9%)	72 (40.7%)	
Pathologic N stage, n (%)			0.666
N0	26 (14.9%)	24 (13.8%)	
N1	60 (34.5%)	64 (36.8%)	
Pathologic M stage, n (%)			0.371
M0	39 (45.9%)	41 (48.2%)	
M1	4 (4.7%)	1 (1.2%)	
Pathologic stage, n (%)			0.693
Stage I&Stage II	82 (46.6%)	86 (48.9%)	
Stage III&Stage IV	5 (2.8%)	3 (1.7%)	
Histologic grade, n (%)			0.037
G1&G2	63 (35.6%)	26 (14.7%)	
G3&G4	24 (13.6%)	64 (36.2%)	
OS event, n (%)			0.03
Alive	50 (27.9%)	36 (20.1%)	
Dead	39 (21.8%)	54 (30.2%)	