

Table S1. Correlations among SGCE and differentially expressed genes (DEGs) in CD24^{low}CD44^{high} ALDH1⁺ BCSCs.

Gene name	Pearson-correlation	P value	Sample size
C1R	0.415	9.59E-47	1 093
KIT	0.4116	6.16E-46	1 093
FZD7	0.3755	6.30E-38	1 093
NTRK3	0.3614	4.72E-35	1 093
LAMA2	0.3503	6.53E-33	1 093
LRP1	0.3501	7.11E-33	1 093
EGFR	0.345	6.47E-32	1 093
BMP2	0.3356	3.53E-30	1 093
PTCH1	0.3287	5.85E-29	1 093
SHC4	0.3282	7.38E-29	1 093
COL5A1	0.3251	2.53E-28	1 093
COL1A1	0.3218	9.44E-28	1 093
WNT5B	0.3218	9.29E-28	1 093
TUBB2B	0.3018	1.91E-24	1 093
IL1R1	0.2837	1.13E-21	1 093
EFNA5	0.2678	2.09E-19	1 093
ELF5	0.2651	4.92E-19	1 093
DAPK1	0.2528	2.15E-17	1 093
IL6	0.2515	3.13E-17	1 093
FZD9	0.2372	1.92E-15	1 093
TLR2	0.233	6.06E-15	1 093
SERPINE1	0.233	6.18E-15	1 093
PLCE1	0.2281	2.29E-14	1 093
SOCS3	0.2206	1.61E-13	1 093
THBS1	0.2159	5.46E-13	1 093

Genes are highly expressed in CD24^{low}CD44^{high}ALDH1⁺ BCSCs ^[1]. We analyzed correlations among SGCE and target genes using LinkedOmics (<http://www.linkedomics.org/login.php>) ^[2].

Table S2. Primers and shRNA sequences used in this paper.

Primer	Primer sequence
SGCE-sh#1-F	CCGGACCTGGATGGCTTCGATATATCTCGAGATATA TCGAAGCCATCCAGGTTTTTTTG
SGCE-sh#1-R	AATTCAAAAAACCTGGATGGCTTCGATATATCTCG AGATATATCGAAGCCATCCAGGT
SGCE-sh#2-F	CCGGATTGAGATGTAGTCAAGAAATCTCGAGATTT CTTGACTACATCTCAA TTTTTTG

SGCE-sh#2-R	AATTCAAAAAATTGAGATGTAGTCAAGAAATCTCG AGA TTTCTTGACTACATCTCAAT
sh-luc-F	GATCCGTCCAGATTGTCCGCAACTACTTCCTGTCA GATAGTTGCGGACAATCTGGACTTTTTG
sh-luc-R	AATTCAAAAAGTCCAGATTGTCCGCAACTATCTGA CAGGAAGTAGTTGCGGACAATCTGGACG
sh-c-Cbl-F	GATCCGAGCTTTCGACAGGCTCTACTTCCTGTCAG ATAGAGCCTGTCGAAAGCTCTTTTTG
sh-c-Cbl-R	AATTCAAAAAGAGCTTTCGACAGGCTCTA TCTGACAGGAAGTAGAGCCTGTCGAAAGCTCG
EGFR-sh#1-F	GATCCGAACATAACATCCTTGGGATTCTTCCTGTC AGAAATCCCAAGGATGTTATGTTCTTTTTG
EGFR-sh#1-R	AATTCAAAAAGAACATAACATCCTTGGGATTCTG ACAGGAAGAATCCCAAGGATGTTATGTTG
EGFR-sh#2-F	GATCCGAAGGAACTGAATTCAAATTCTTCCTGTC AGAAATTTGAATTCAGTTTCCTTCTTTTTG-
EGFR-sh#2-R	AATTCAAAAAGAAGGAACTGAATTCAAATTTCT GACAGGAAGAATTTGAATTCAGTTTCCTTCG
siSGCE#1-F	GGAAAUCAUACCUCCUUUATT
siSGCE#1-R	TTCCUUUAGUAUGGAGGAAAU
siSGCE#2-F	ACCUGGAUGGCUUCGAUAUAUTT
siSGCE#2-R	TTUGGACCUACCGAAGCUAUUA
q-RT-SGCE-F	GGTTCTTGAGACTTTCTTGGC
q-RT-SGCE-R	ATGACATAAACGCCCTCCTTC
q-RT-ITGA3-F	CTACCACAACGAGATGTGCAA
q-RT-ITGA3-R	CCGAAGTACACAGTGTTCTGG
q-RT-ITGA6-F	GGCGGTGTTATGTCCTGAGTC
q-RT-ITGA6-R	AATCGCCCATCACAAAAGCTC
q-RT-ITGB4-F	CTCCACCGAGTCAGCCTTC

q-RT-ITGB4-R	CGGGTAGTCCTGTGTCCTGTA
q-RT-LAMA3-F	CACCGGGATATTTTCGGGAATC
q-RT-LAMA3-R	AGCTGTCGCAATCATCACATT
q-RT-LAMB3-F	CCAAAGGTGCGACTGCAATG
q-RT-LAMB3-R	AGTTCTTGCCTTCGGTGTGG
q-RT-LAMC2-F	CAAAGGTTCTCTTAGTGCTCGAT
q-RT-LAMC2-R	CACTTGGAGTCTAGCAGTCTCT
q-RT-FN-F	GAGAATGGACCTGCAAGCCCA
q-RT-FN-R	AGTGCAAGTGATGCGTCCGC
q-RT-COL17A1-F	ACCAGCAATGGCTATGCTAAAA
q-R -COL17A1-R	GCCTCGTGTGCTTCCAGTT
q-RT-GAPDH-F	AGCCACATCGCTCAGACAC
q-RT-GAPDH-R	GCCCAATACGACCAAATCC
q-RT-ACTA2-F:	CTATGAGGGCTATGCCTTGCC
q-RT-ACTA2-R	GCTCAGCAGTAGTAACGAAGGA
q-RT-S100A2-F:	GCCAAGAGGGCGACAAGTT
q-RT-S100A2-R	AGGAAAACAGCATACTCCTGGA
q-RT-S100A4-F:	GATGAGCAACTTGGACAGCAA
q-RT-S100A4-R	CTGGGCTGCTTATCTGGGAAG

- [1] M. Liu, Y. Liu, L. Deng, D. Wang, X. He, L. Zhou, M. S. Wicha, F. Bai, S. Liu, *Mol. Cancer* **2018**, 17, 65.
- [2] S. V. Vasaikar, P. Straub, J. Wang, B. Zhang, *Nucleic Acids Res* **2018**, 46, D956.

Figure S1. UMAP plots of TNBC epithelial cells.

A-G) UMAP plots of TNBC epithelial cells showing expression levels of CD24, CD44, ALDH1A3, SGCE, EGFR, ACVR2A, and PLXDC2.

Figure S2. SGCE promotes self-renewal of BCSCs.

A-B) Relapse-free survival (RFS) (A) and distal metastasis-free survival (DMFS) (B) of SGCE in various types of breast cancer. C) Relative expression of SGCE in various types of breast cancer using TCGA database. D) Assay of CD24^{low}CD44^{high} population upon SGCE knockdown in HCC1937 cells. E) Knockdown efficiencies of SGCE in TNBC cell lines. F) Overexpression efficiencies of SGCE by PCDH plasmid containing Flag tag in TNBC cell lines. (**) $P < 0.01$.

Figure S3. Loss of SGCE increases chemotherapy sensitivity of breast cancer through BCSCs.

A-B) Assay of ALDH⁺ population upon SGCE knockdown in HCC1806 (A) and MDA-MB-231 cells (B). C) Assay of CD24^{low}CD44^{high} population upon SGCE knockdown in HCC1806 cells. D-E) Clonal formation assay upon SGCE knockdown in HCC1806 (D) and MDA-MB-231 (E) cells. F-G) Tumorsphere assay upon SGCE knockdown in HCC1806 (F) and MDA-MB-231 (G) cells. H-I) Cell viability (%) in HCC1806 (H) and MDA-MB-231 cells (I) after treatment with various concentrations of cisplatin. J-Q) Tumorsphere (J), clonal formation (K), ALDH ratio (L), CD24^{low}CD44^{high} ratio (M), and their percentage calculations (N for J, O for K, P for L, and Q for M) following treatment with doxorubicin, paclitaxel, and cisplatin in SGCE-depleted HCC1806 cells. (*) $P < 0.05$; (**) $P < 0.01$. Dox: doxorubicin; Ptx: paclitaxel; Cis: cisplatin.

Figure S4. SGCE promotes ECM deposition.

A) Co-expression network of SGCE and ECM-related genes in basal-like breast cancer based on TCGA database. B) Heatmap of ECM receptor interaction in SGCE-knockdown HCC1806 cells. C) KEGG pathway analysis of SGCE in basal-like patients from TCGA database. Top 10% positively related genes with SGCE were selected for KEGG pathway analysis. D) KEGG pathway analysis in SGCE-knockdown HCC1806 cells.

Figure S5. SGCE regulates BCSCs and ECM through EGFR.

A) Western blot of EGFR and related genes in SGCE-knockdown MDA-MB-231 cells. B-D) ALDH (B), tumorsphere (C), and clonal formation (D) analyses with EGFR overexpression in SGCE-knockdown MDA-MB-231 cells. E) mRNA levels of ECM-related genes in EGFR knockdown cells. F) Protein levels in ECM-related genes in SGCE-depleted cells with EGFR overexpression in MDA-MB-231 cells. (*) $P < 0.05$; (**) $P < 0.01$; (***) $P < 0.001$.

Figure S6. SGCE regulates EGFR lysosomal degradation.

A) Immunoblotting analysis of EGFR in SGCE-knockdown cells with internalization inhibitors. B) Immunoblotting analysis of EGFR in SGCE-knockdown MDA-MB-231 cells with NH_4Cl treatment. C) FACS analysis of EGFR in SGCE-knockdown MDA-MB-231 cells with NH_4Cl treatment. D) Immunofluorescence staining of EGFR and LAMP1 in MDA-MB-231 cells. E-F) Immunoblotting analysis of EGFR in SGCE-knockdown MDA-MB-231 (E) and HCC1806 (F) cells after MG132

treatment. G) Negative co-immunoprecipitation results of EGFR and SGCE. H) Negative co-immunoprecipitation results of EGFR and GRB2.

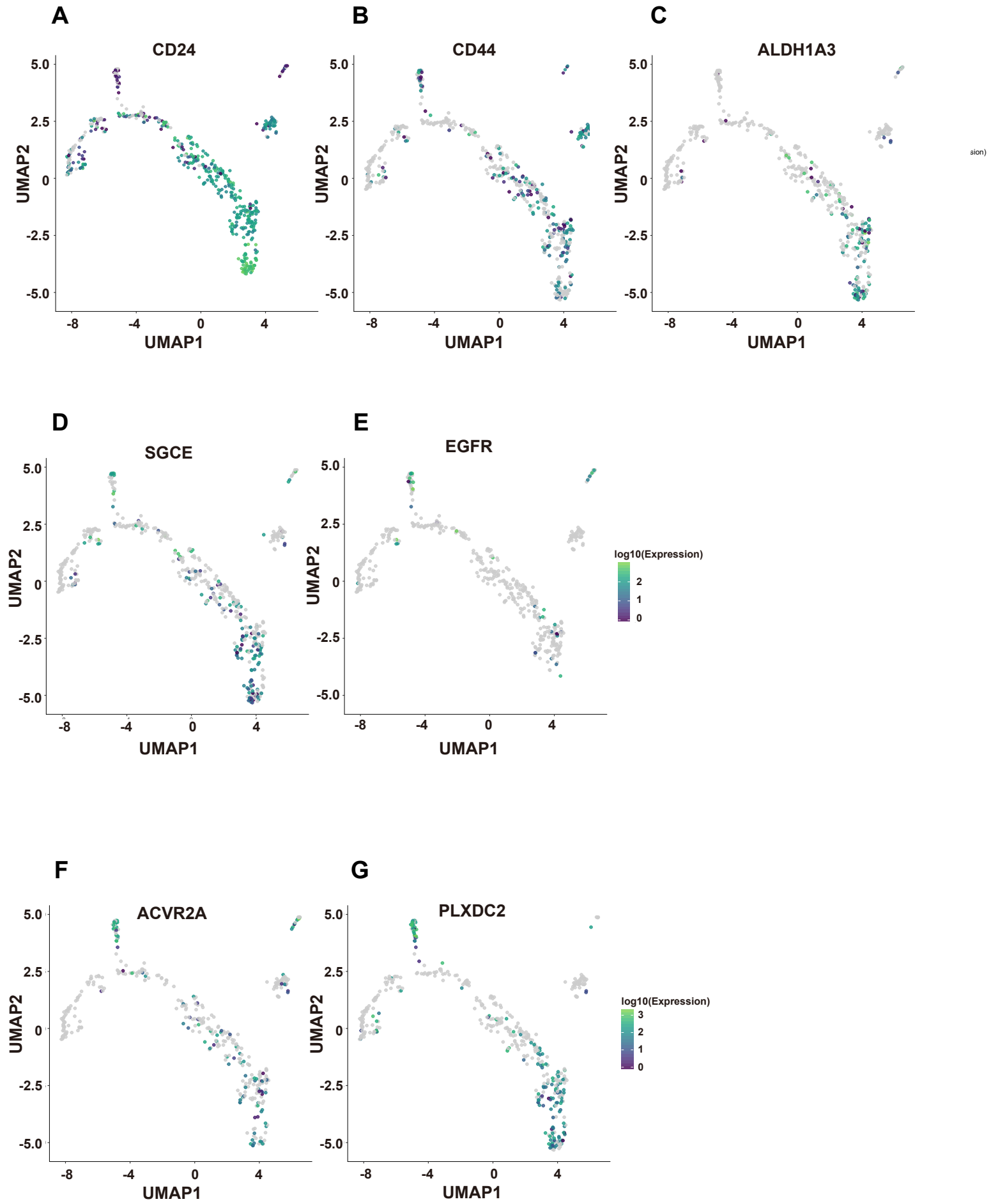
Figure S7. SGCE promotes drug resistance-targeted EGFR.

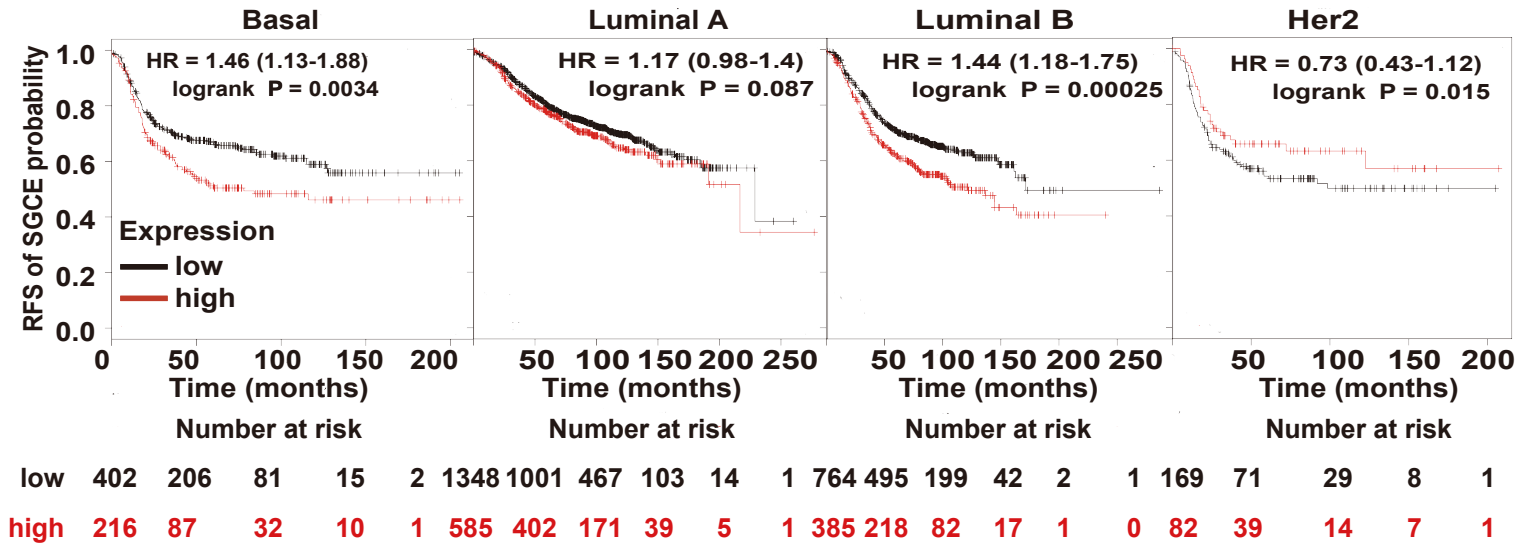
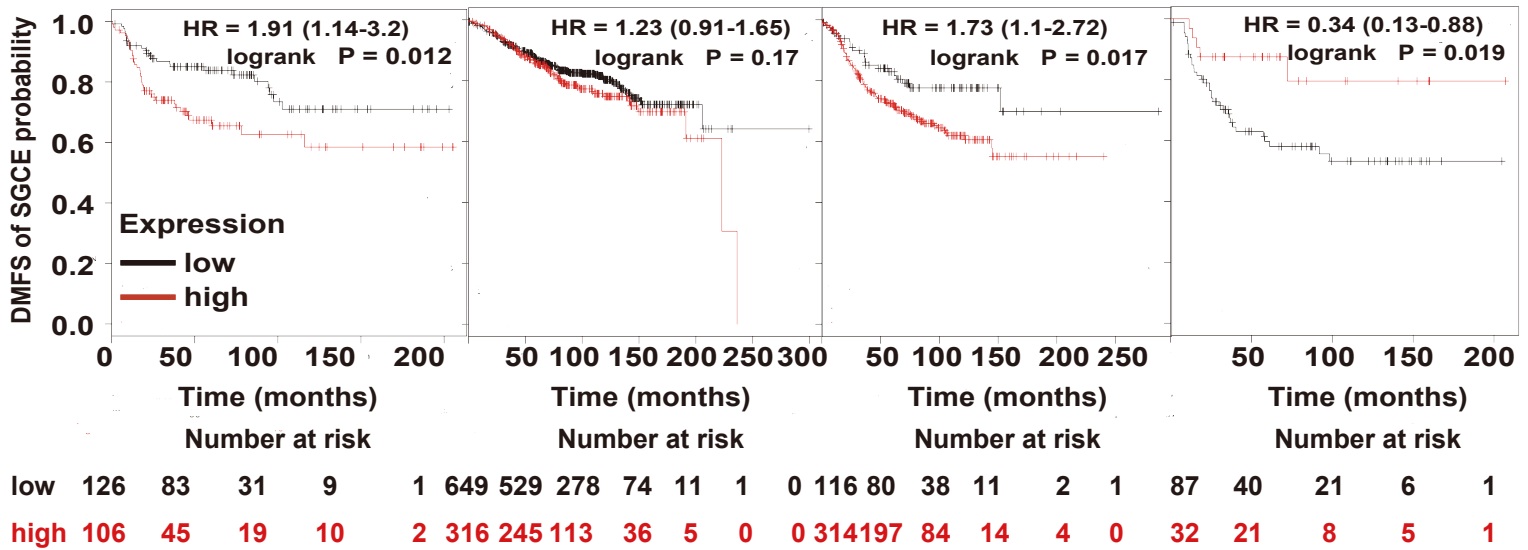
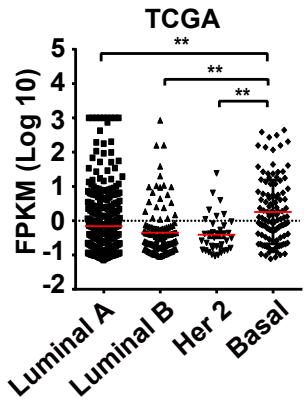
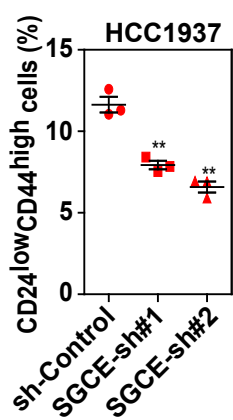
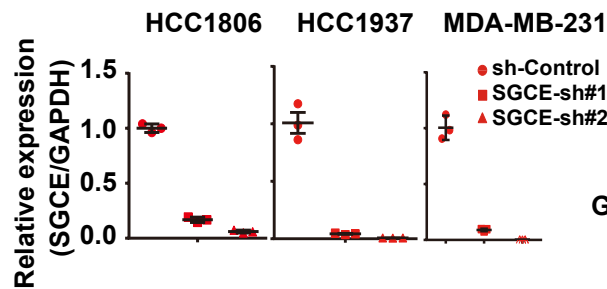
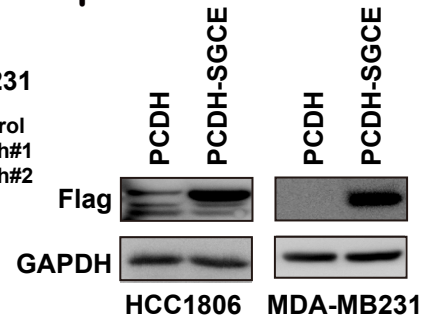
A) GSEA of NF- κ B signaling pathway in SGCE-knockdown HCC1806 cell lines. B-C) Immunoblotting analysis of c-Met in SGCE-knockdown cell lines. D-E) Immunoblotting analysis of NF- κ B signaling pathway in SGCE-knockdown TNBC cell lines. F-I) Drug sensitivity experiments in gefitinib- and lapatinib-resistant cells in comparison to parental cells. J-K) Drug sensitivity experiments following SGCE knockdown in lapatinib-resistant HCC1806 (J) and MDA-MB-231 (K) cell lines.

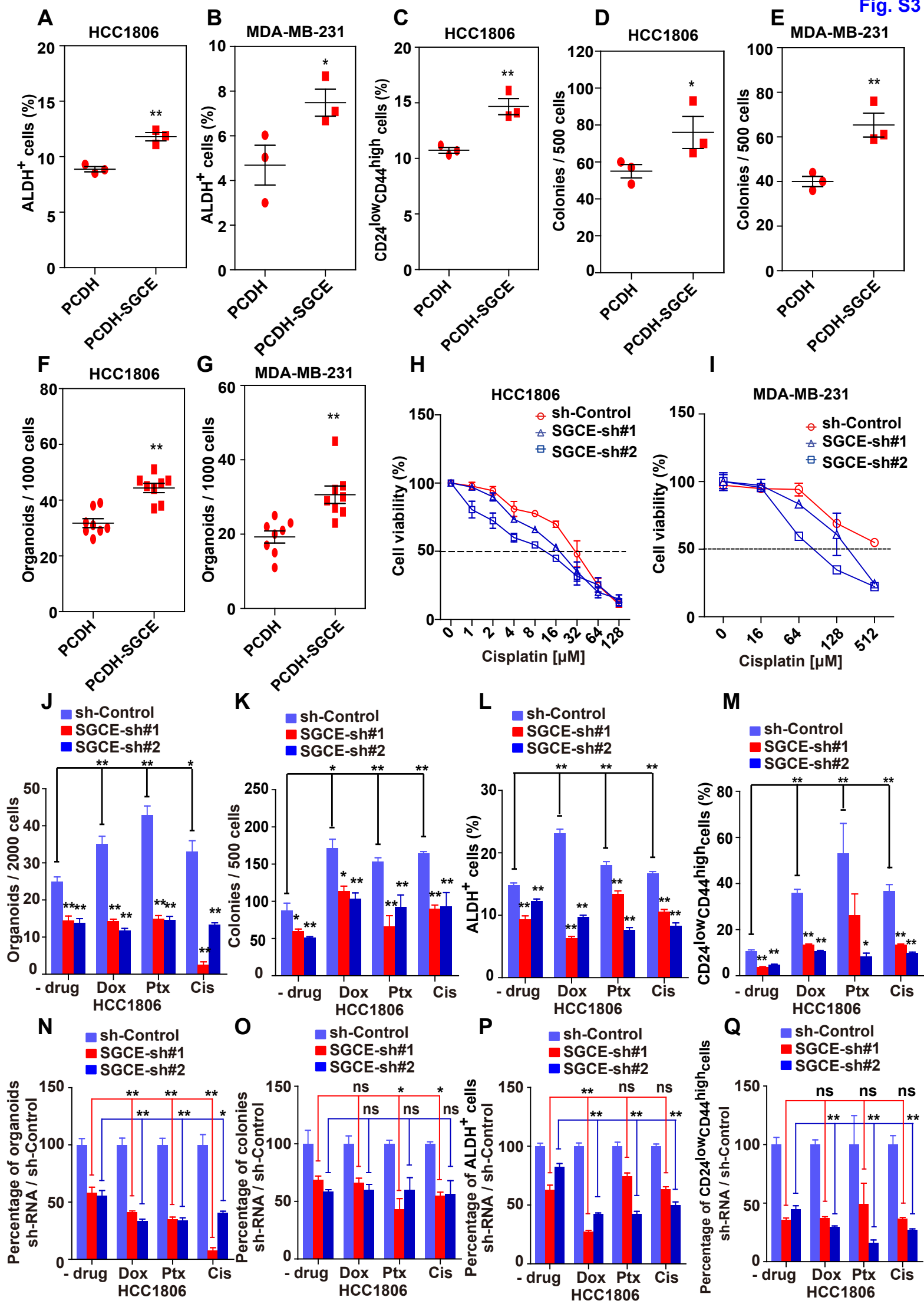
Figure S8. Signaling pathways regulated by SGCE.

A) Luciferase activities with overexpression of SGCE. HEK293 cells were co-transfected with SGCE, luciferase-responsive plasmid, and Renilla (10:10:1, total 0.22 μ g). Cells were collected with dual-luciferase reporter assay system. B-C) Immunoblotting analysis of stemness-related genes in SGCE-knockdown cell lines. D-E) NF- κ B signaling pathway in TNBC cell lines. F) Immunoblotting analysis of EGFR in gefitinib-resistant cells. G) Co-immunoprecipitation results of EGFR and c-Cbl in gefitinib-resistant cells.

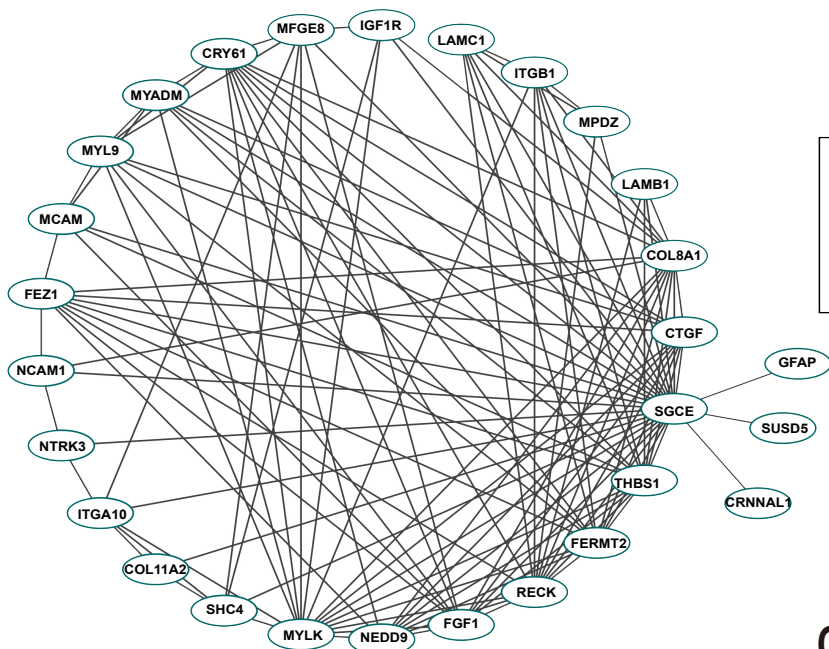
Fig. S1



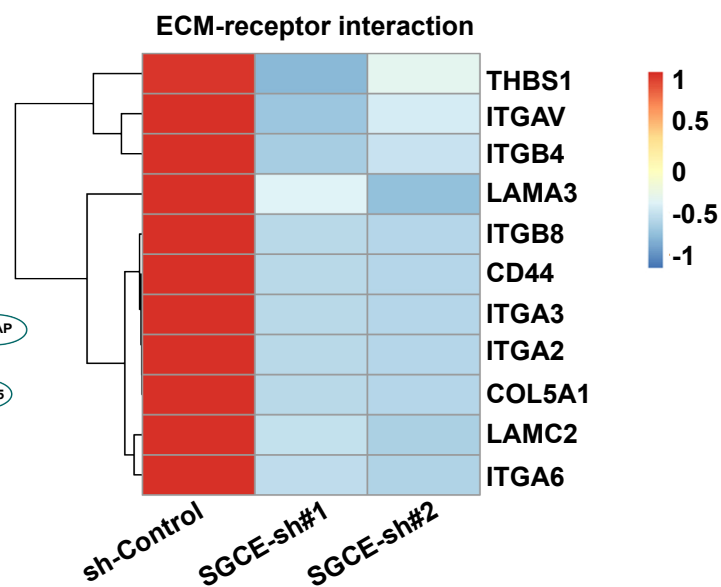
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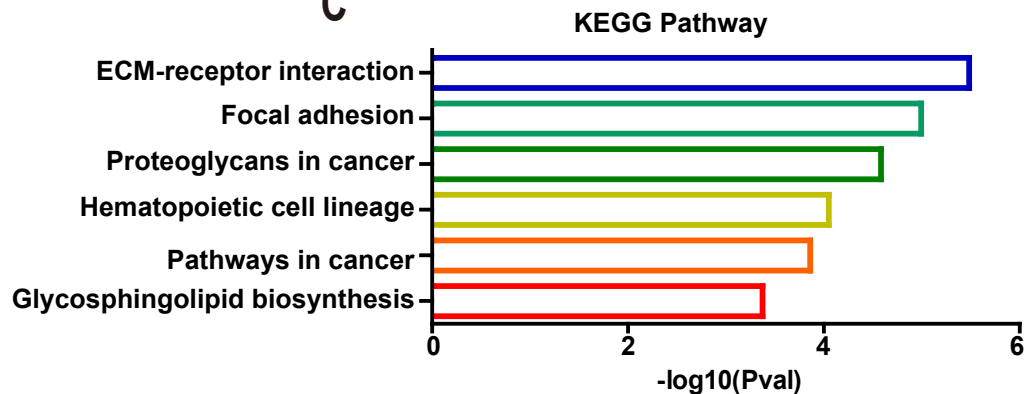
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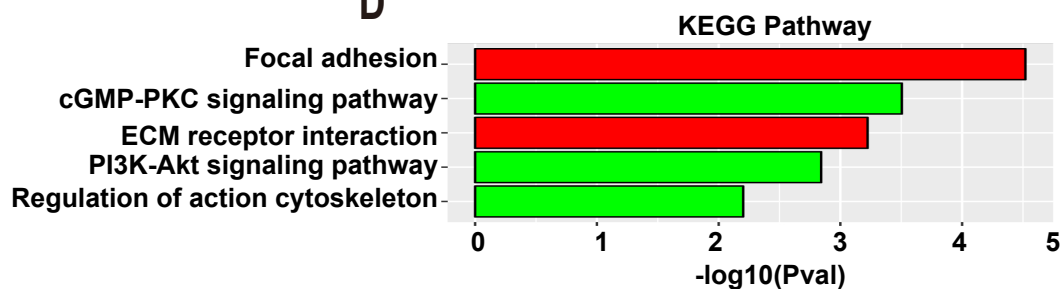
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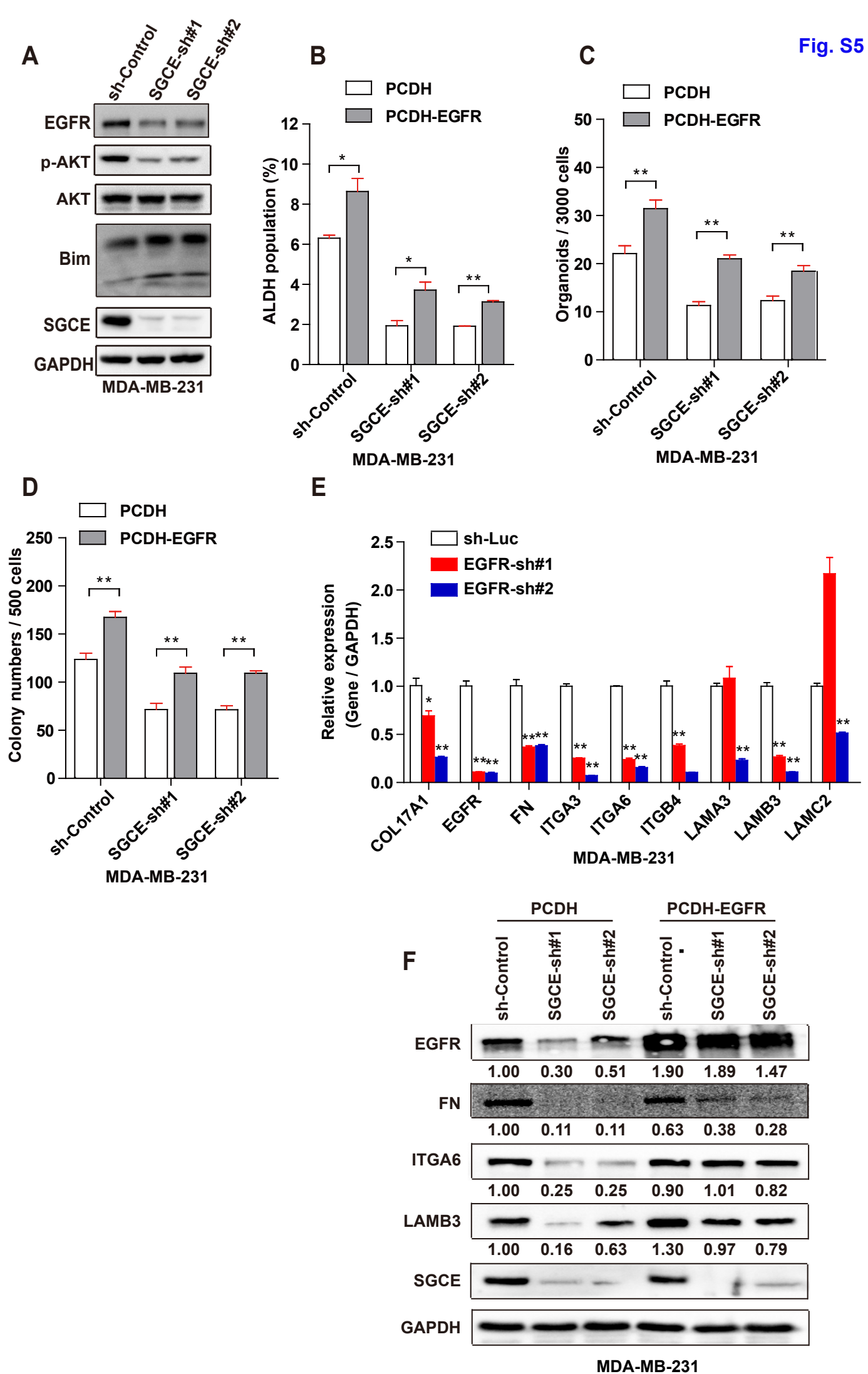


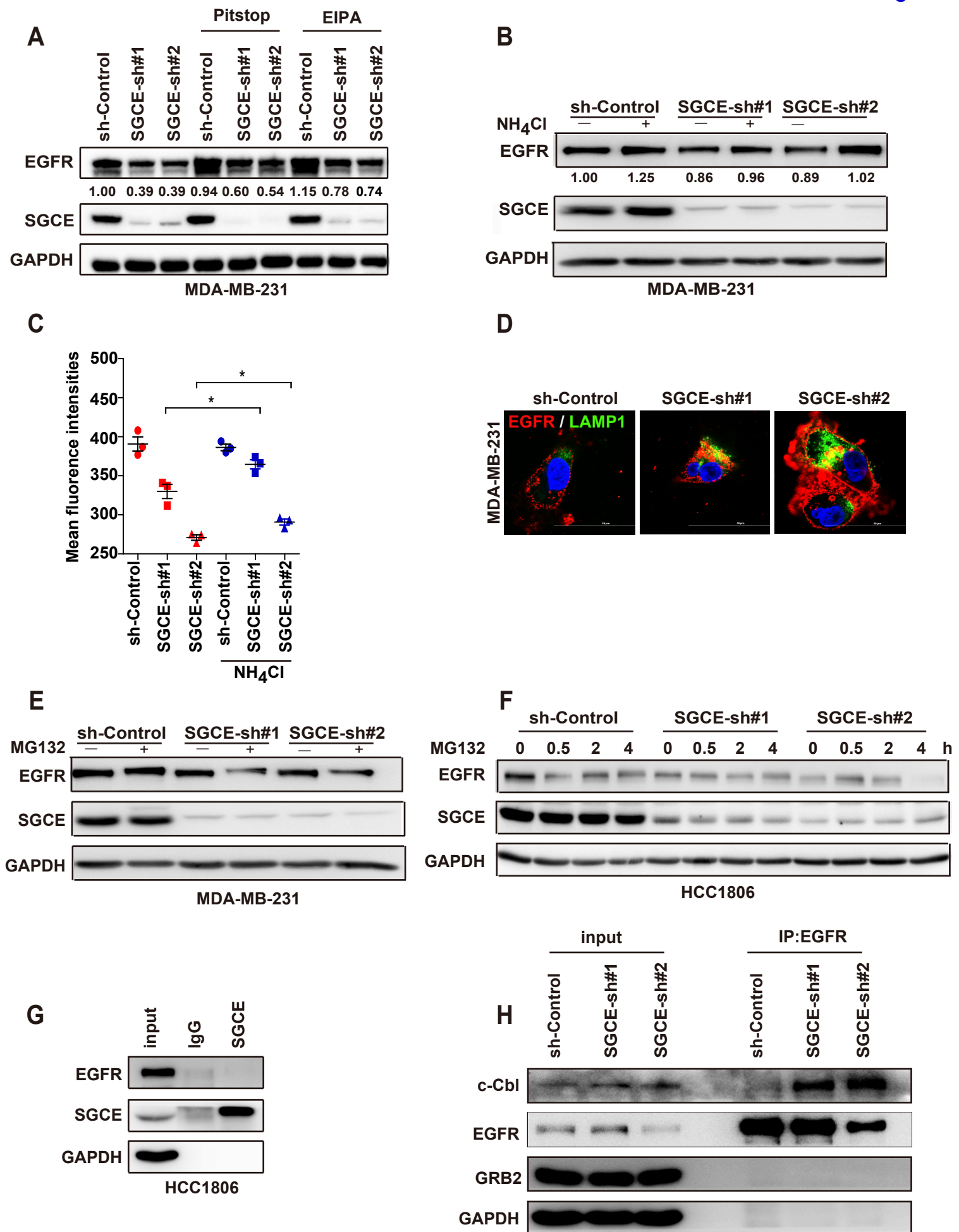
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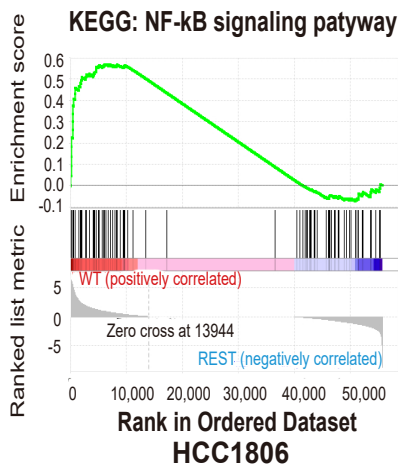
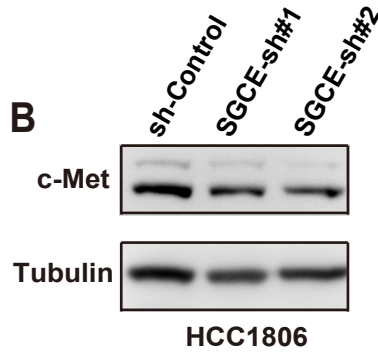
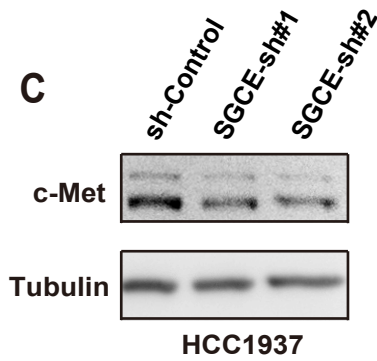
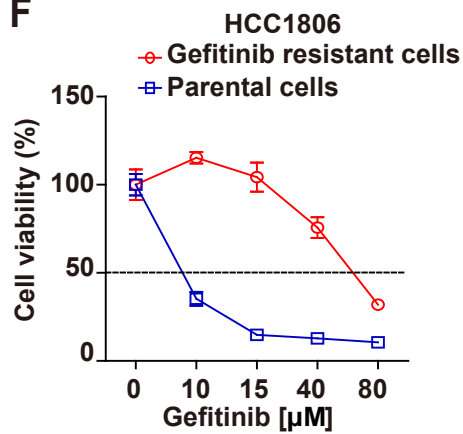
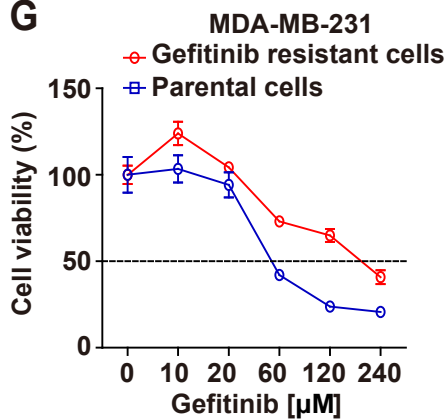
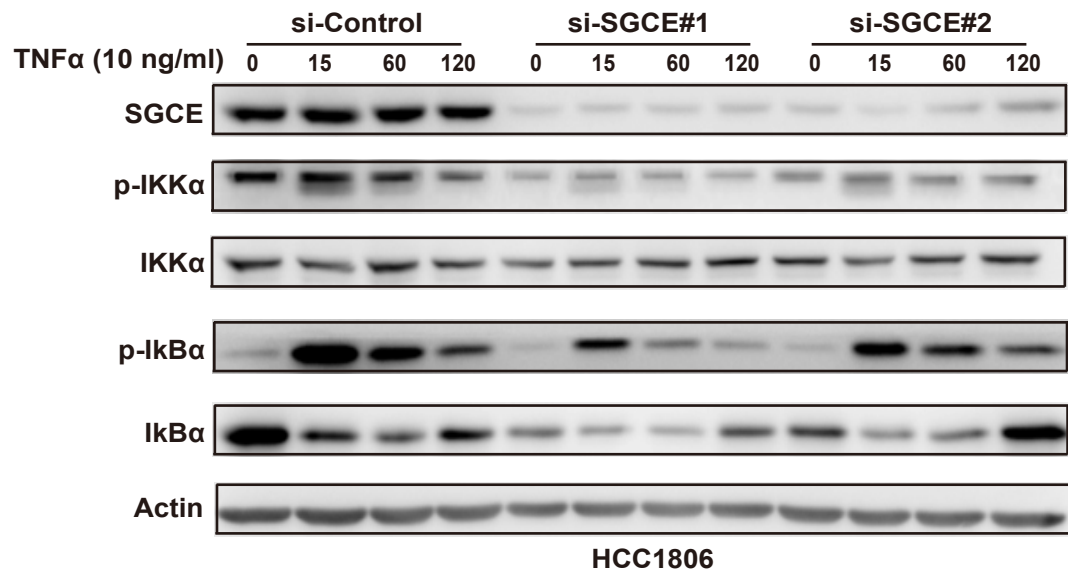
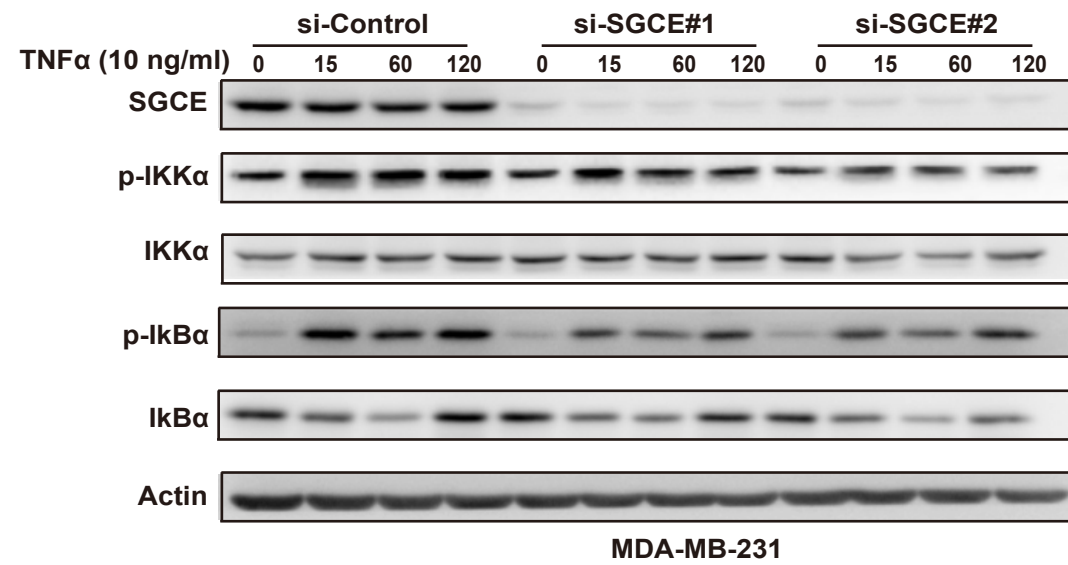
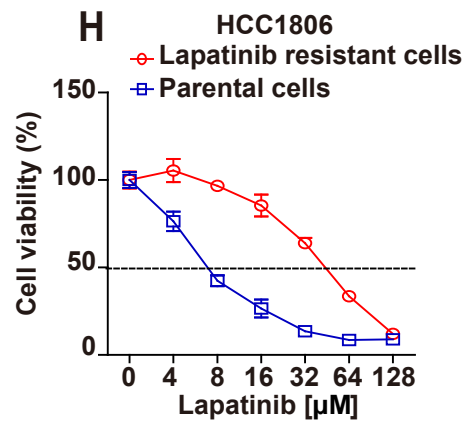
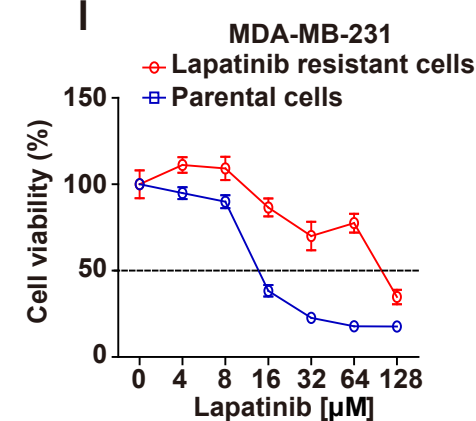
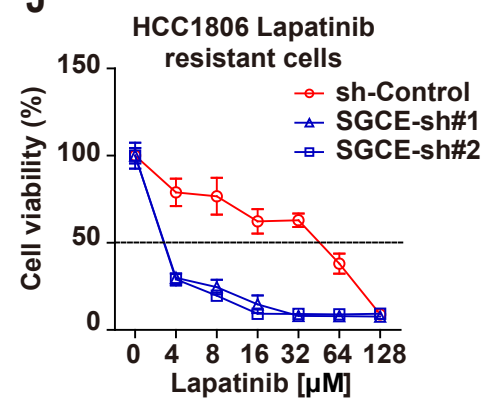


D







A**B****C****F****G****D****E****H****I****J****K**