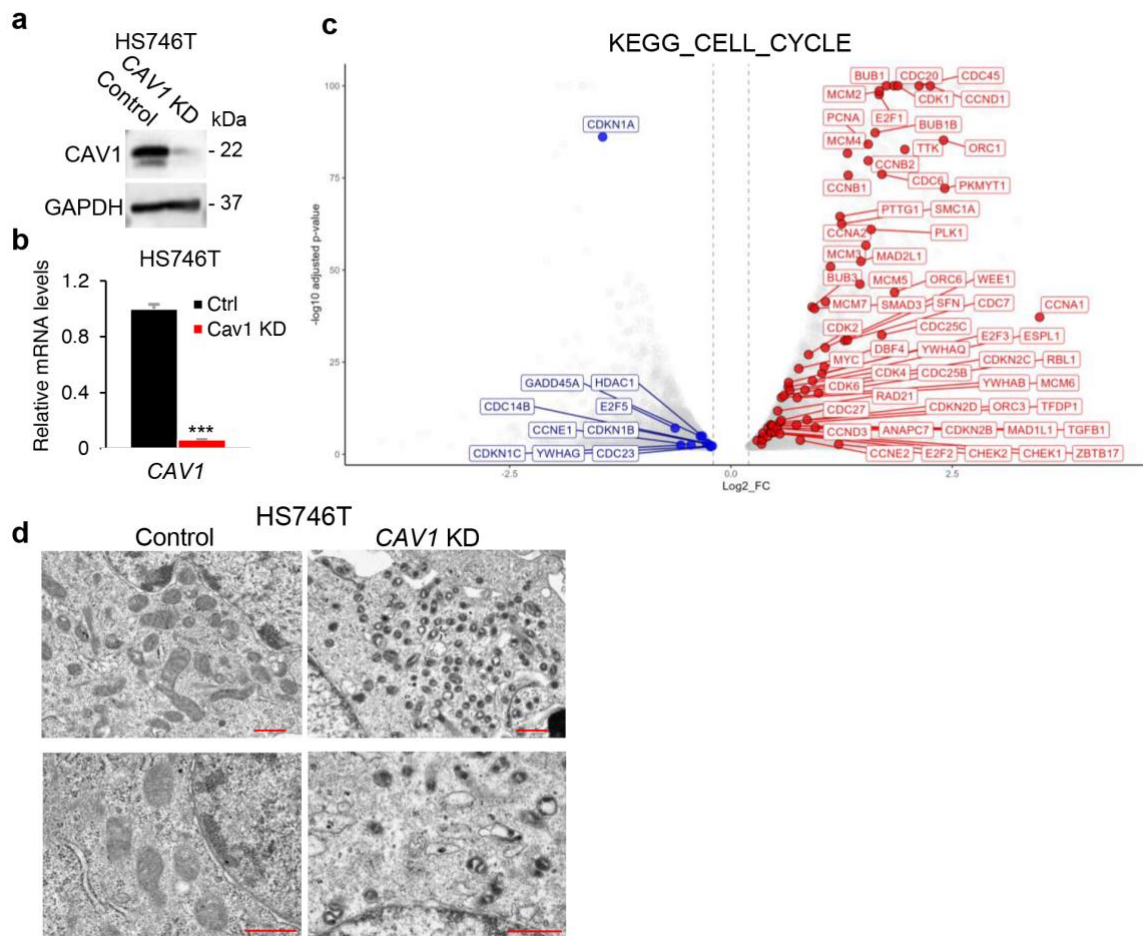
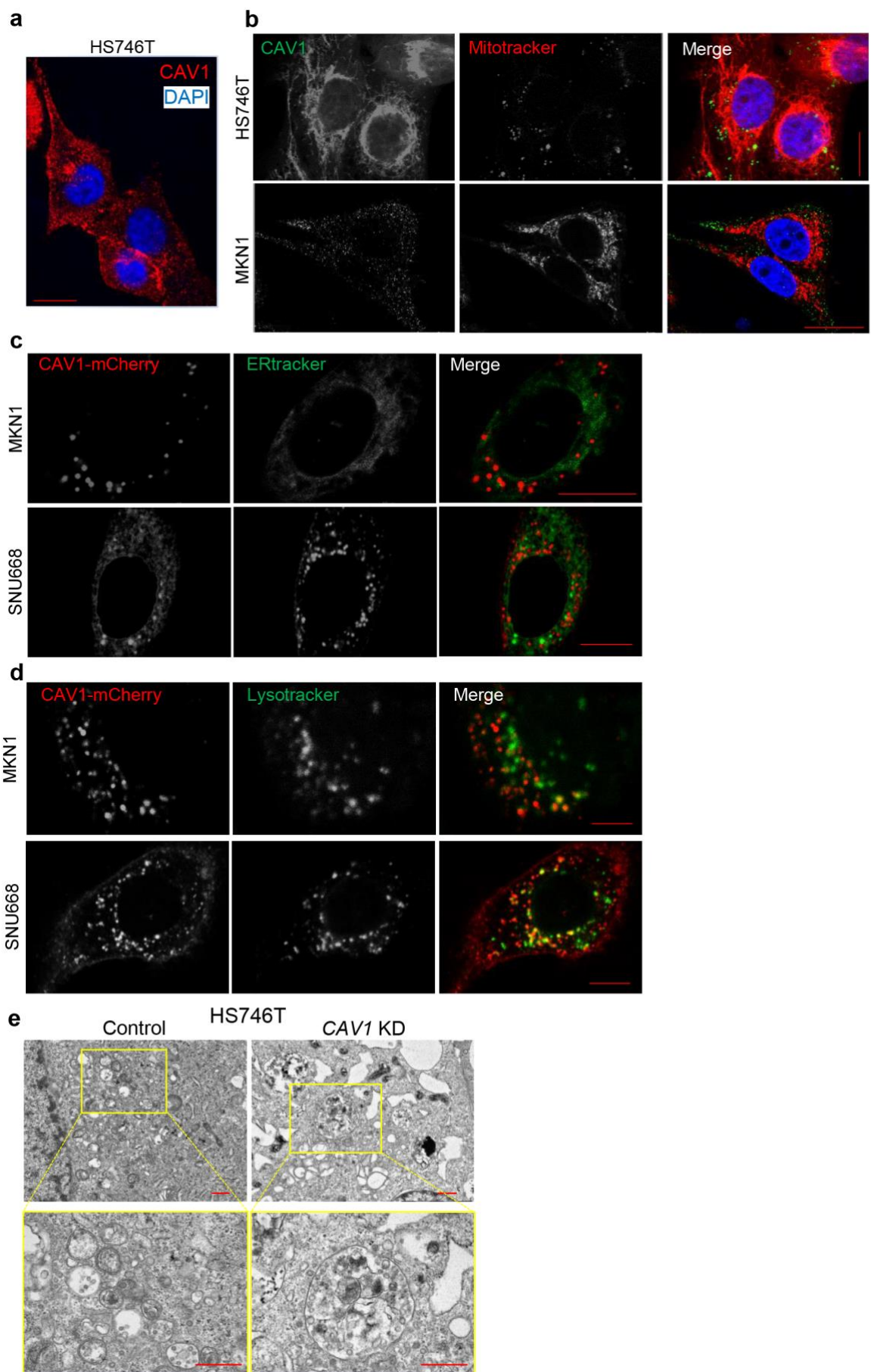


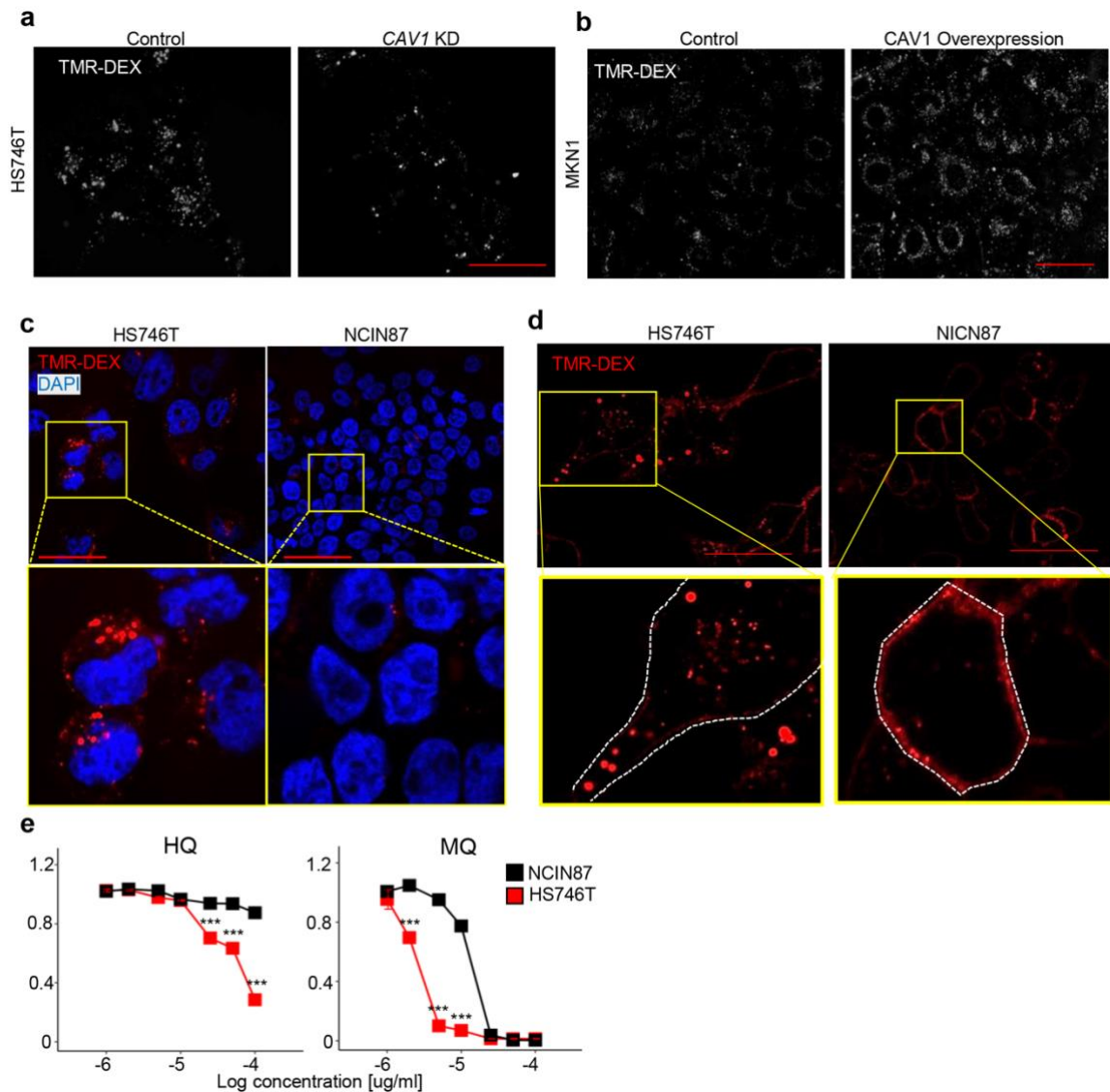


Supplementary Fig. 1 Inhibition of CAV1 is fatal to SEM-type GC cells.

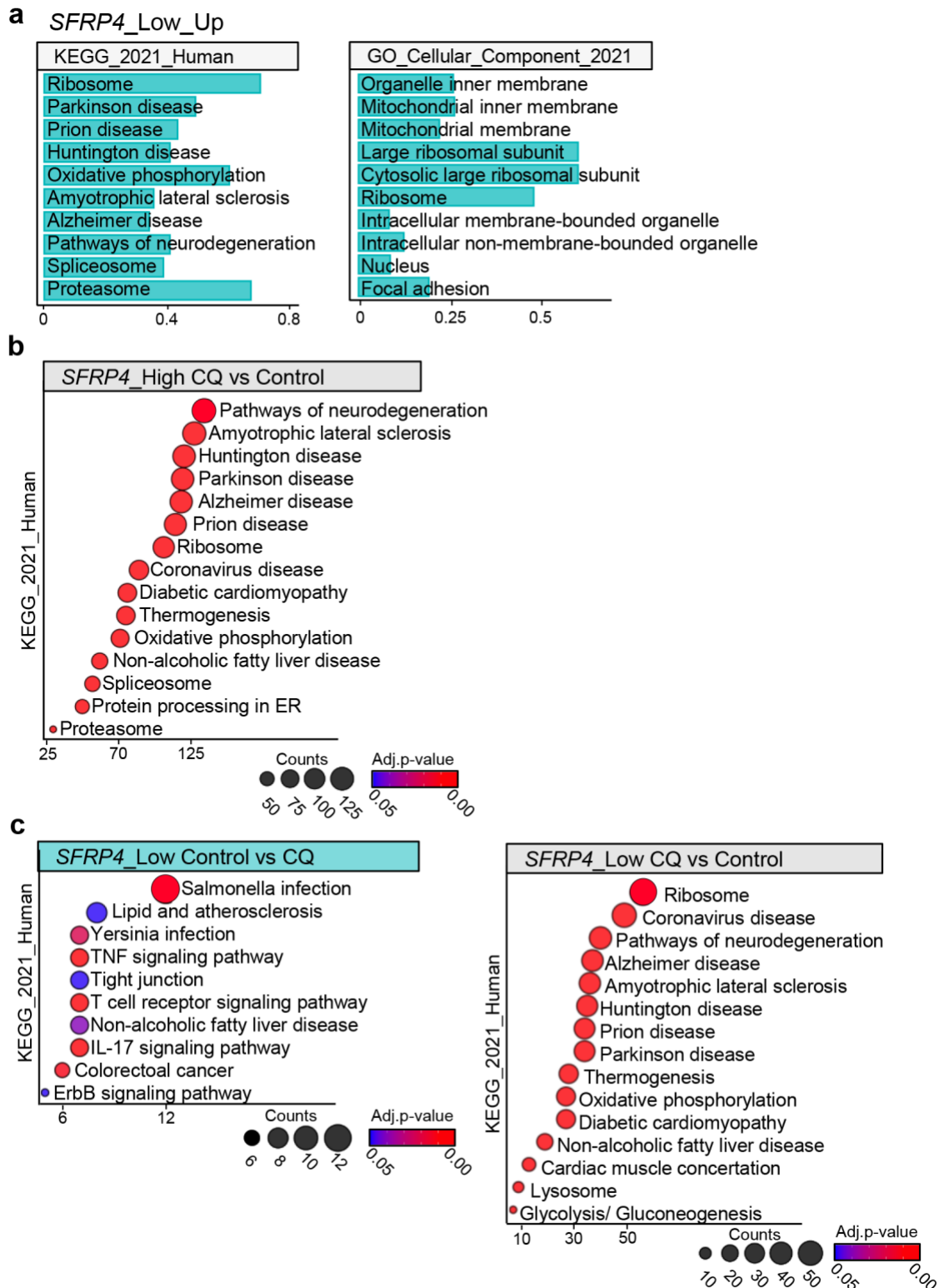
(a and b) Expression of CAV1 in HS746T after knockdown with siRNA at the protein levels **(a)** and the relative mRNA levels **(b)**. **(c)** Volcano plot representing gene sets of KEGG_CELL_CYCLE in the DEGs of HS746T after *CAVI* knockdown (blue; down-regulated, red; up-regulated, log2 fold change > 0.2, adjusted p-value < 0.01). **(d)** TEM images showing damaged mitochondria in *CAVI*-knockdowned HS746T. N; nucleus, arrow; mitochondria. Scale bar, 1 μ m. Data represent mean $\pm$ SD. ** p < 0.01; *** p < 0.001; two-tailed t test.



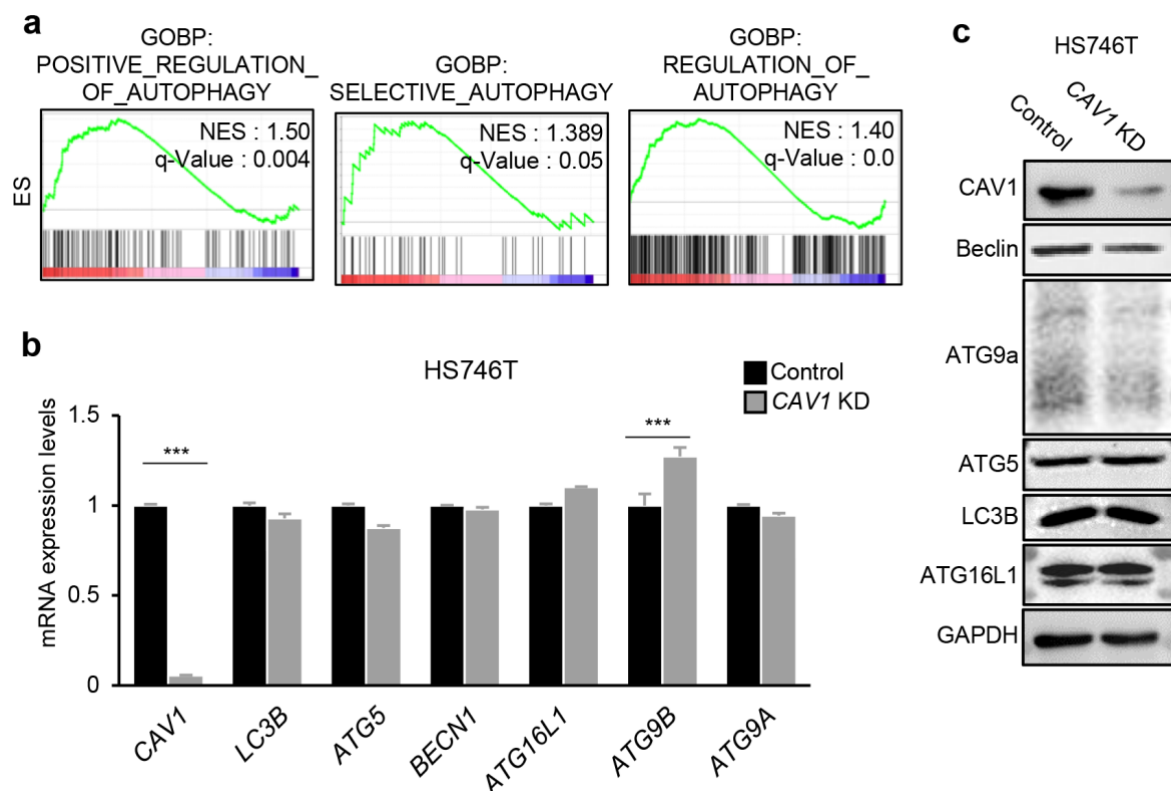
Supplementary Fig. 2 CAV1 is in lysosome in SEM-type GC cells. (a) A Confocal image of CAV1(red) and DAPI (blue) in HS746T. Scale bars, 20 μ m. (b) Confocal images of HS746T and MKN1 expressing mCherry-CAV1(left), Mito-tracker(middle). Merged images are a two-channel combination of original image pairs (mCherry-cav1; green, Mito-tracker; red, DAPI; blue, right). Scale bar, 20 μ m. (c) Live cell images of SNU668 and MKN1 expressing mCherry-CAV1(left), ER-tracker(middle). Merged images (mCherry-CAV1; red, ER-tracker; green, right). Scale bar 5 μ m,10 μ m respectively. (d) Live cell images of SNU668 and MKN1 expressing mCherry-CAV1(left), lysotracker (middle) and. Merged images (mCherry-CAV1; green, lysotracker; red, right). Scale bar 20 μ m and 5 μ m, respectively. (e) TEM images showing damaged lysosome in *CAV1*-knockdowned HS746T. N; nucleus, arrow; mitochondria. Scale bar, 1 μ m



Supplementary Fig. 3 CAV1-mediated endocytosis is up-regulated in SEM-type GC cells and is effectively regressed by lysosome inhibitors. (a and b) TMR-DEX uptake assay of (a) CAV1-knockdown HS746T and (b) CAV1-overexpressed MKN1. Scale bars, 50 μ m. (n=2/group). (c and d) Confocal images of HS746T and NCIN87 after TMR-DEX uptake assay. The cells were imaged fixed (c) or alive (d) (TMR-DEX; red, DAPI; blue). Scale bars, 50 μ m. (e) The IC₅₀ values of Hydroxy-chloroquine (HQ), and Mefloquine (MQ) treatment for HS746T(red) and NCIN87(black), respectively. Data represent mean $\pm$ SD. ** $p < 0.01$; *** $p < 0.001$; two-tailed t test.



Supplementary Fig. 4 Effect of CQ on *SFRP4*-high and -low clusters in SEM-type GC tumoroid, respectively (a) KEGG and GOCC analysis with DEGs of *SFRP4*-low compared to -high cluster (b) KEGG analysis with DEGs of control group compared to CQ. *SFRP4*-high cluster were classified and analyzed. (c) KEGG analysis with DEGs of CQ group compared to Control. *SFRP4*-low cluster were classified and analyzed. The DEGs used for each analysis had a p- value of less than 0.01, and the log2 fold change was greater than 0.1.



Supplementary Fig. 5 The role of CAV1 is not related to autophagy, but to endocytosis.

(a) Gene Set Enrichment Analysis for GOBP_POSITIVE_REGULATION_OF_AUTOPHAGY, GOBP_SELECTIVE_AUTOPHAGY, and REGULATION_OF_AUTOPHAGY from MsigDB v7.0 in SEM type GC cells compared to non-SEM type GC cells. **(b and c)** Expression of CAV1 in HS746T after knockdown with siRNA at the relative mRNA levels **(b)** and the protein levels **(c)**. Data represent mean $\pm$ SD. ** $p < 0.01$; *** $p < 0.001$; two-tailed t test.