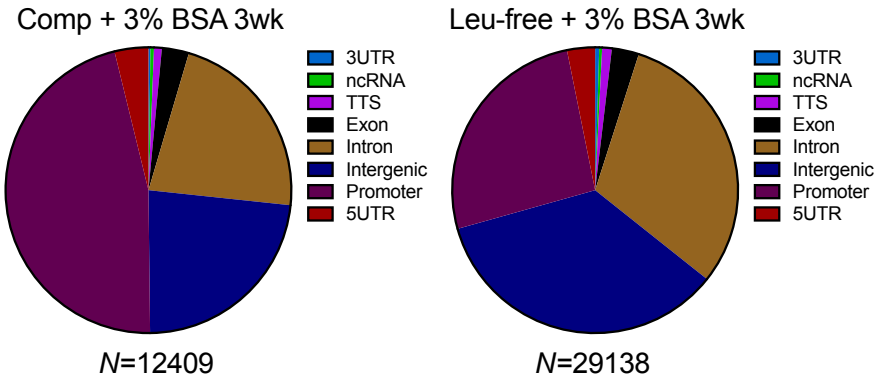
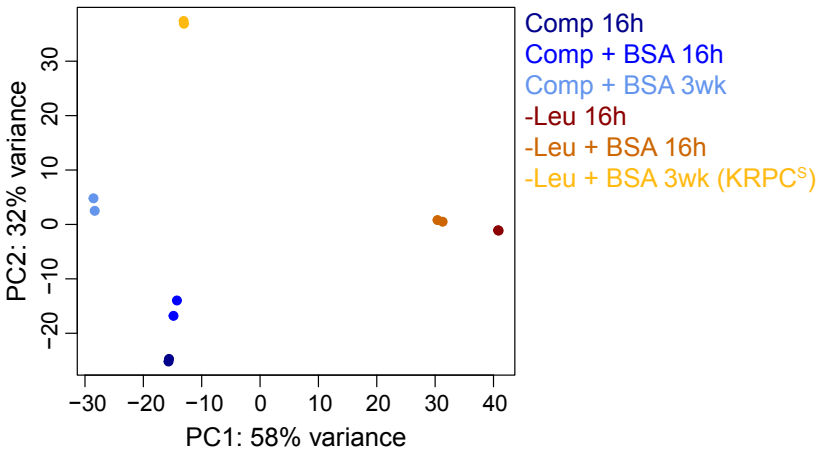
Supplemental Fig. S1

A

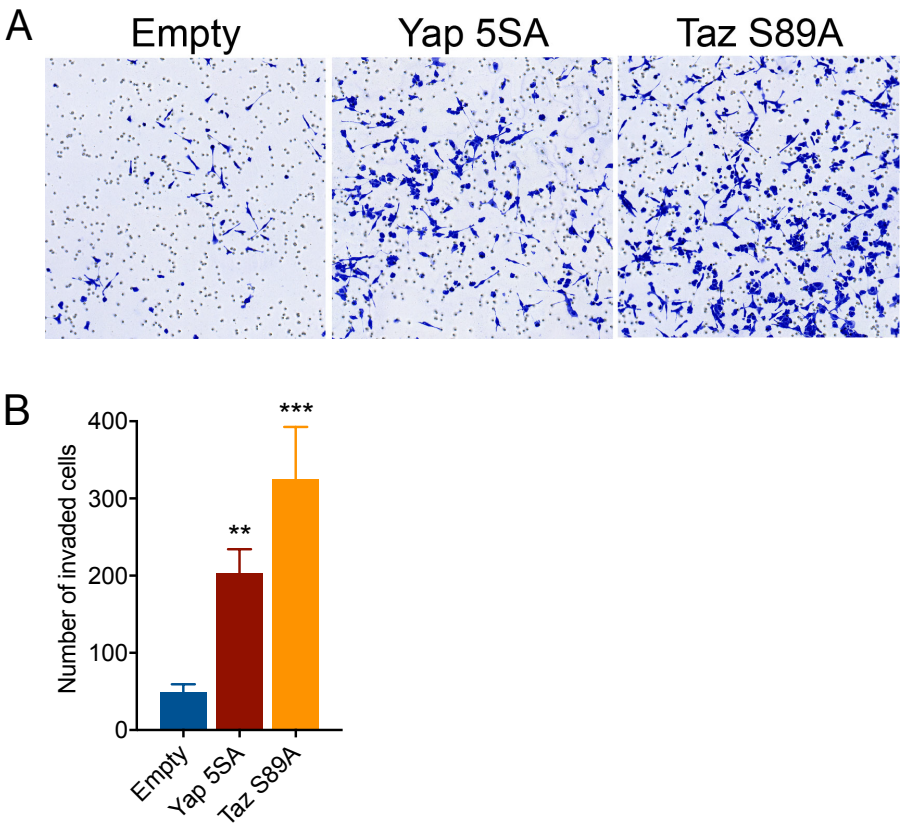


B



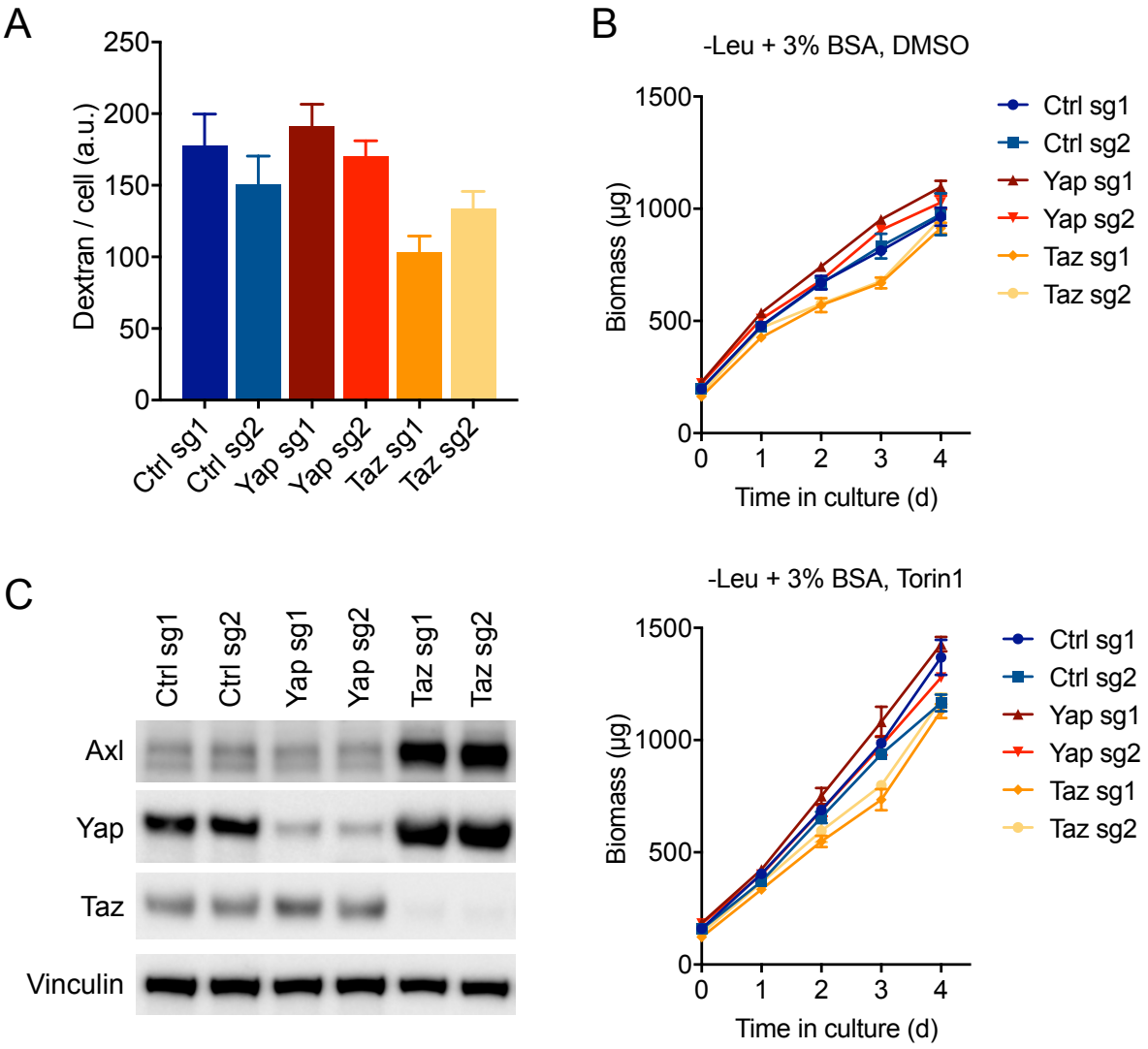
Supplemental Fig. S1: Selection for extracellular protein-dependent growth is associated with increased chromatin accessibility and a distinct transcriptional program.
a, Pie chart depicting frequency of ATAC-seq peaks within annotated genomic regions in KRPC cells cultured for 21d in either complete or leucine-free medium supplemented with 3% BSA. **b**, Principal component analysis (PCA) plot of gene expression KRPC cells cultured in either complete or leucine-free medium, for 16h or 21d +/- 3% BSA, as measured by RNA-seq, in biological duplicates.

Supplemental Fig. S2



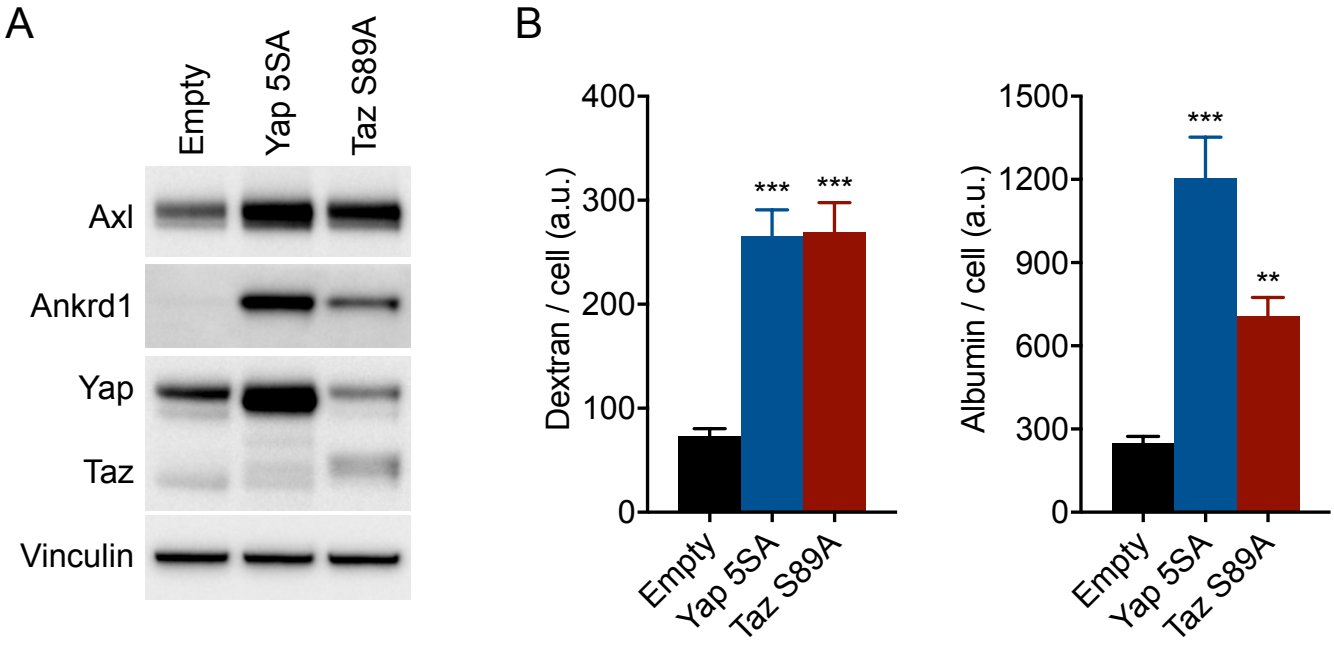
Supplemental Fig. S2: Expression of constitutively nuclear Yap/Taz promotes invasion by PDA cells. **a**, Bright-field images showing invasion of parental KRPC cells transduced with retroviruses expressing doxycycline-inducible Yap or Taz cDNAs across matrigel-coated membranes. Assay was performed after 48h of culture in 100 ng/ml doxycycline. **b**, Bar plot represents mean +/- s.e.m. of number of invaded cells counted per field across three biological replicates. ***p < 0.0001, **p < 0.005, one-way ANOVA.

Supplemental Fig. S3



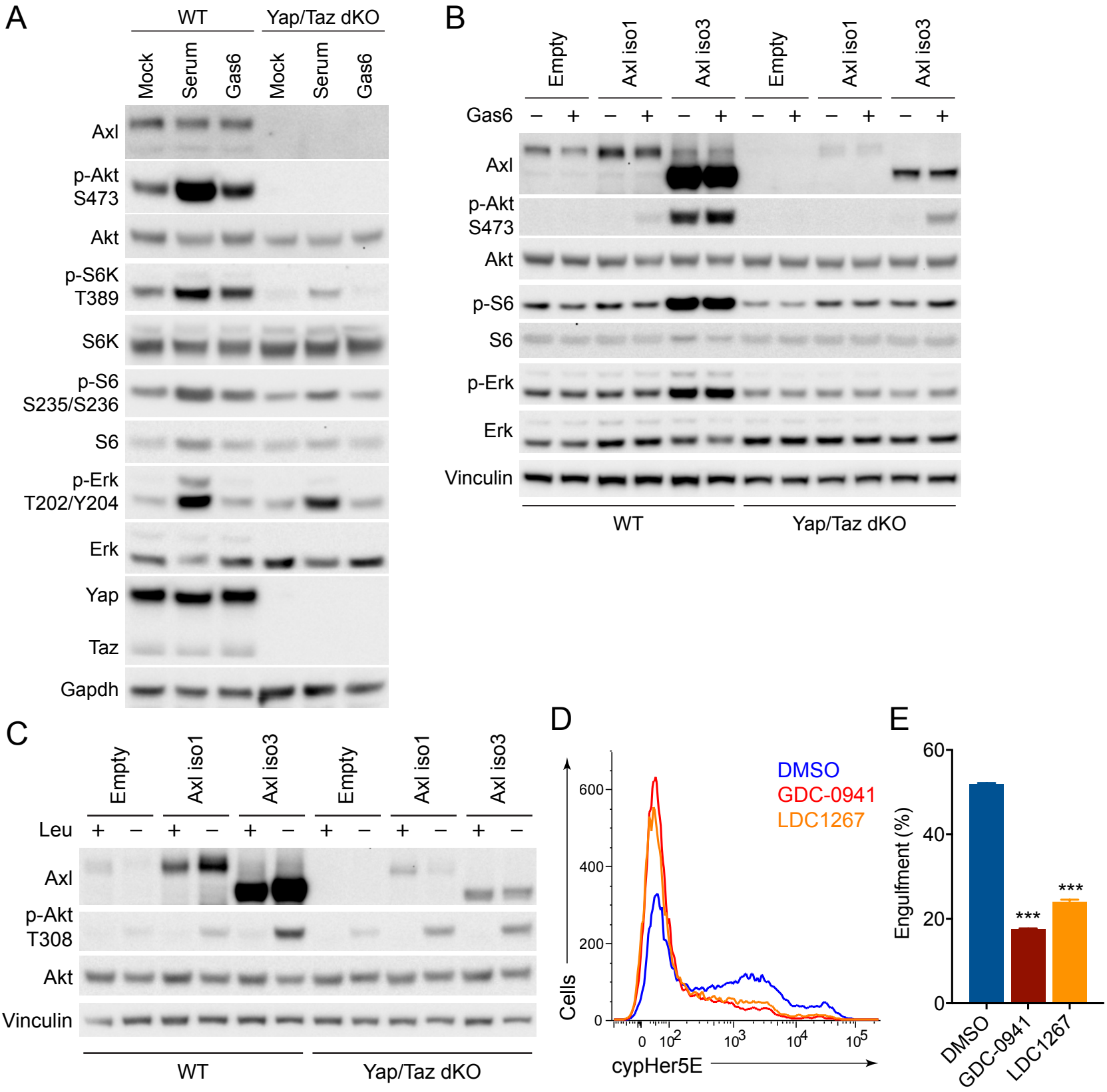
Supplemental Fig. S3: Loss of Yap or Taz alone does not impair macropinocytosis or albumin-dependent growth in PDA cells.
a, Uptake of fluorescent dextran by KRPC cells transduced with lentiviruses expressing Cas9 and sgRNAs targeting Yap, Taz or control genomic loci, as measured by fluorescence confocal microscopy. Bars represent mean +/- s.e.m. fluorescence intensity per cell, across 12 fields of view. **b**, Growth of KRPC cells transduced with lentiviruses expressing Cas9 and sgRNAs targeting Yap, Taz or control genomic loci in leucine-free medium supplemented with 3% BSA +/- Torin1 (250nM). **c**, Immunoblot of whole cell lysates from KRPC cells transduced with lentiviruses expressing Cas9 and sgRNAs targeting Yap, Taz or control genomic loci.

Supplemental Fig. S4



Supplemental Fig. S4: Expression of constitutively nuclear Yap/Taz promotes macropinocytosis and albumin uptake in Ras wild-type PDA cells.
a, Immunoblot of whole cell lysates from BxPC-3 cells transduced with retroviruses expressing a dox-inducible Yap or Taz mutant cDNA or empty vector control after 24h of culture in 100ng/ml doxycycline. **b**, Bar plots represent mean uptake per cell +/- s.e.m. of fluorescently-labeled 70kDa dextran (left) and albumin (right) in 30 min by BxPC-3 cells described in **a**.

Supplemental Fig. S5



Supplemental Fig. S5: Yap/Taz-dependent expression of Axl promotes PI3-kinase activation and uptake of necrotic cells through macropinocytosis. a, Immunoblot of whole cell lysates from WT or Yap/Taz dKO KRPC cells following 8h of serum starvation in 0.1% FBS and 15 min treatment +/- 10% FBS or recombinant Gas6 (400 ng/ml). **b**, Immunoblot of whole cell lysates from WT or Yap/Taz dKO KRPC cells transduced with retroviruses expressing a doxycycline-inducible mouse Axl (isoform 1 or 3) cDNA, following 8h of serum starvation in 0.1% FBS and 15 min +/- recombinant Gas6 (400 ng/ml). Cells were cultured in 100 ng/ml doxycycline for 16h prior and during serum starvation. **c**, Immunoblot of whole cell lysates from from WT or Yap/Taz dKO KRPC cells transduced with retroviruses expressing a doxycycline-inducible mouse Axl (isoform 1 or 3) cDNA cultured for 24h in complete or leucine-free medium supplemented with 3% BSA and 100 ng/ml doxycycline. **d**, Histogram showing engulfment of cypHer5E-stained necrotic FL5.12 cells by KRPC cells after 4h in the presence of 1μM GDC-0941, 100nM LDC1267 or vehicle, as measured by flow cytometry. Bar plot (**e**) represents mean +/- s.d. of cypHer5E-positive cells from three technical replicates. ***p < 0.0001, one-way ANOVA.