Expanded View Figures

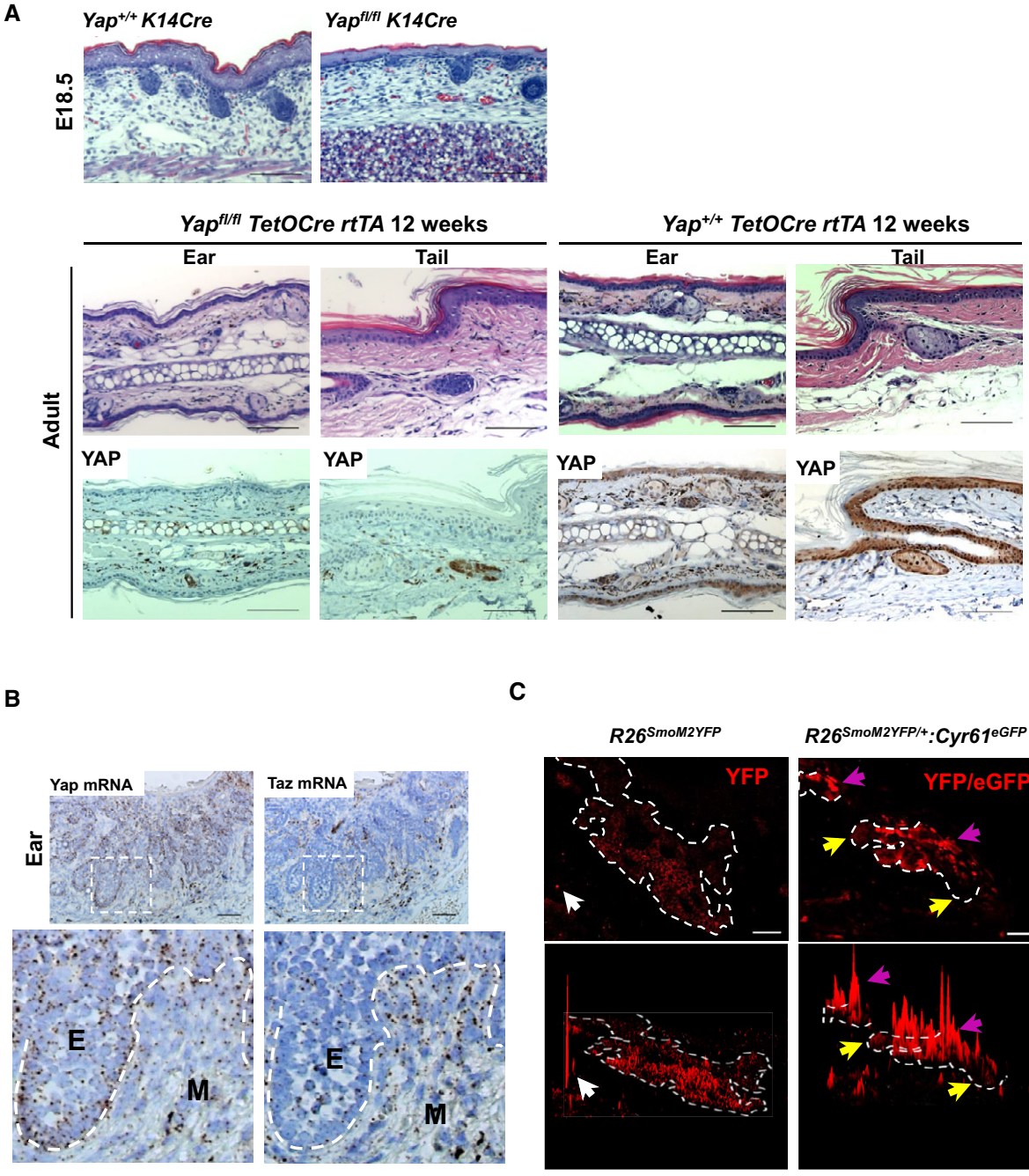


Figure EV1. Homeostatic YAP function in skin epidermis and Yap/Taz expression patterns in BCC.

A Assessment of YAP requirement in embryonic back skin (upper panels) and adult ear and tail epidermis (lower panels). *K14Cre* is used to knockout *Yap* in embryonic epidermis; *TetO-Cre* is activated in 8-week-old mouse using doxycycline for 1 week and tissue analyzed 12 weeks later. Scale bar is 100 μm.

B Yap and Taz mRNA expression (RNAscope) in ear BCC. Dashed lines outline epithelial cells (E). M denotes surrounding mesenchymal cells. Scale bar is 50 μm.

C Immunofluorescent YFP/eGFP pixel intensity histogram in the $R26^{SmoM2YFP/+}$ and $R26^{SmoM2YFP/+}$:$Cyr61^{eGFP}$ mice to visualize differential YFP/eGFP signal in BCC cells. White arrows indicate high YFP/eGFP peak in a non-specific splotch (left panels). Yellow arrows indicate cells with low YFP/eGFP signal; purple arrows indicate cells with high YFP/eGFP signal (right panels). ZEN software was used to generate pixel intensity histograms. Dashed lines in the image outline BCC clones. Scale bar is 50 μm.

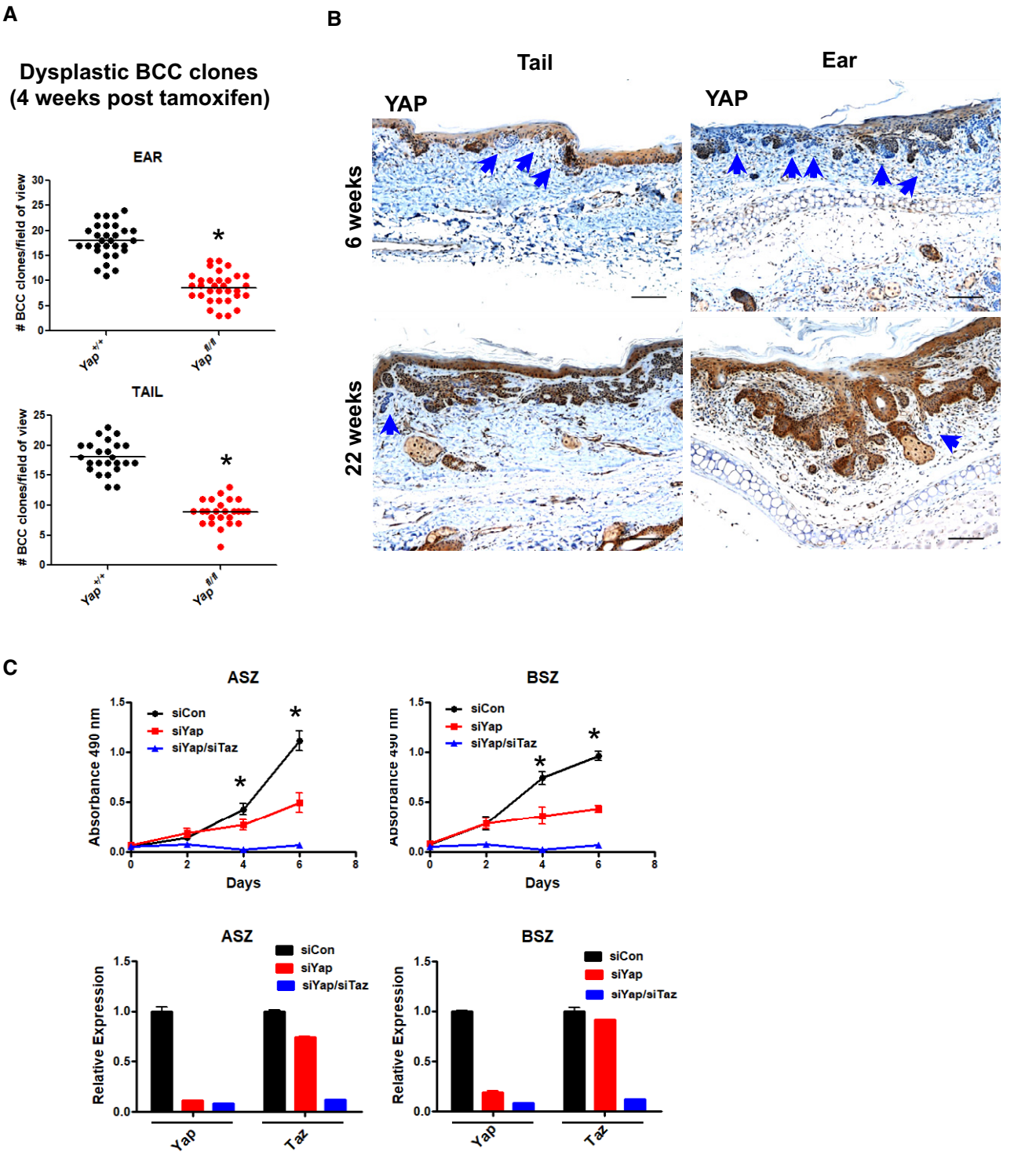


Figure EV2. YAP is required for *in vivo* and *in vitro* BCC growth.

A Quantified number of dysplastic BCC clones per field of view (5× magnification) in ear and tail skin ($Yap^{+/+}$and $Yap^{fl/fl}$ mice) 4 weeks after high-dose tamoxifen administration. Total of three mice per genotype were used, and at least eight clones were counted per tissue section. The groups were compared using Student's *t*-test. $^*P < 0.0001$.

B YAP IHC in ear and tail BCC tumors from $Yap^{fl/fl}$ mice 6 and 25 weeks after high-dose tamoxifen administration. Blue arrows indicate *Yap*-null BCC clones. Scale bar is 100 μm.

C Yap and Yap/Taz RNAi impairs *in vitro* proliferation of ASZ and BSZ mouse BCC cell lines (upper panels). $^*P < 0.05$. qPCR analysis of Yap and Taz knockdown efficiency in ASZ and BSZ mouse BCC cell lines (lower panels).

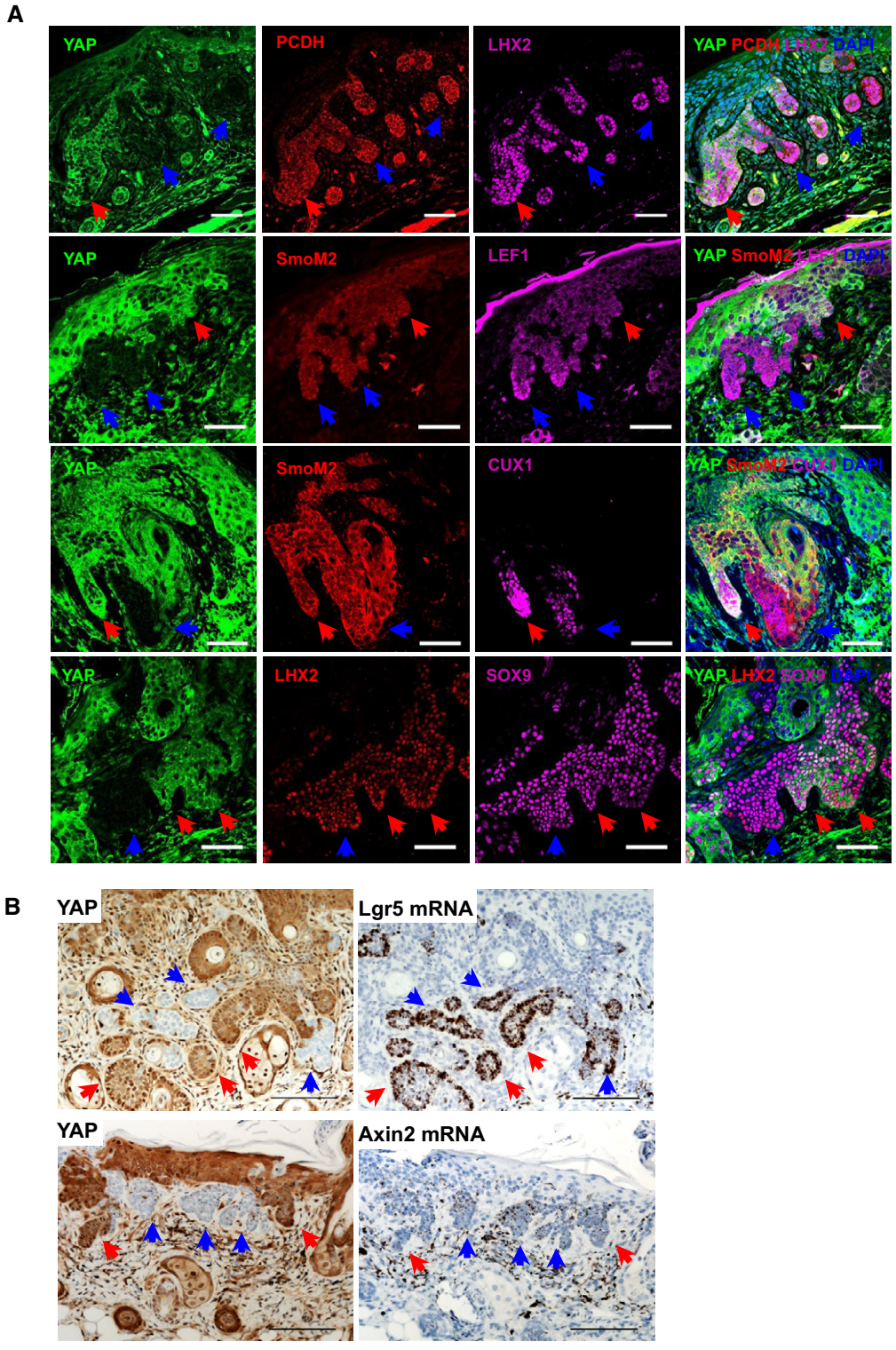


Figure EV3. YAP has no effect on Wnt signaling in BCC.

A Immunofluorescent staining of YAP with SOX9 or embryonic hair follicle phenotype genes (LEF1, CUX1, LHX2, PCDH) in $Yap^{fl/fl}$ BCC. Red arrows indicate YAP-positive clones; blue arrows indicate YAP-negative clones. Scale bar is 50 μm.

B YAP IHC and Lgr5 or Axin2 RNAscope in $Yap^{fl/fl}$ BCC serial sections. Red arrows indicate YAP-positive clones; blue arrows indicate YAP-negative clones. Scale bar is 100 μm.

A

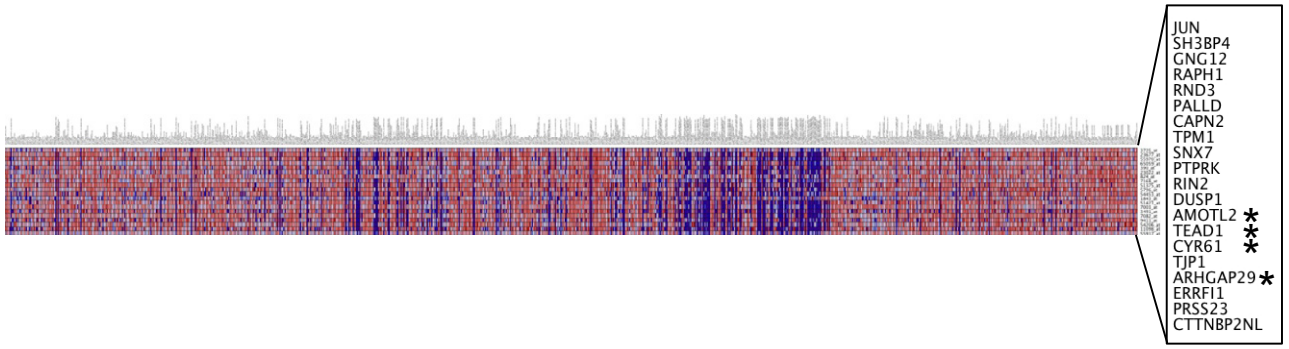
TEAD1 ChIP

Motif	Best match	p value	% of targets
	**TEAD**	1e-1499	33.87
	**AP1**	1e-437	16.65
	**NF1** (halfsite)	1e-116	37.55
	**Br-Z3**	1e-78	23.8
	**Athb24**	1e-52	9.62

TEAD4 ChIP

Motif	Best match	p value	% of targets
	**TEAD**	1e-201	17.06
	**AP1**	1e-184	14.39
	**EGR2**	1e-63	26.63
	**CEBP**	1e-48	46.35
	**NF1**	1e-46	22.99

B



C

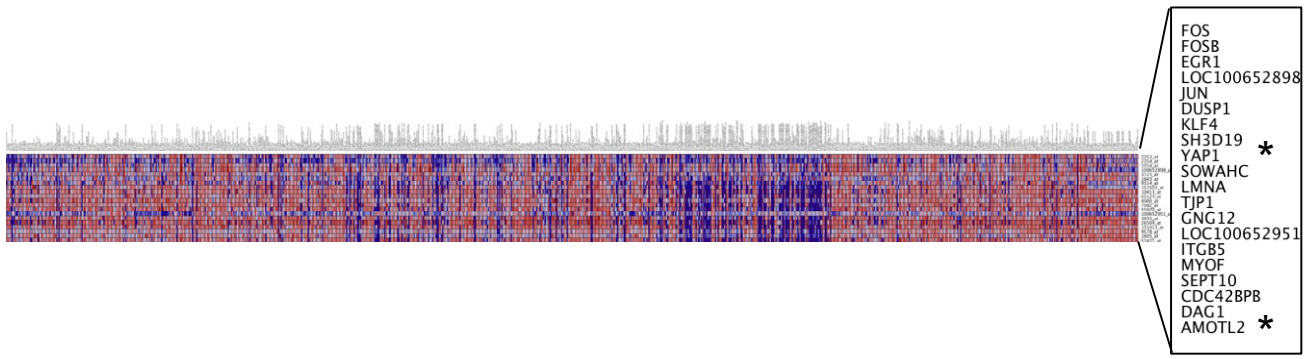


Figure EV4. Bioinformatics analyses to define YAP-dependent programs in BCC.

A Transcription factor motif enrichment from TEAD1 and TEAD4 ChIP in BCC (Homer *de novo* motifs).

B Top 20 genes co-expressed with c-JUN across various cancer cell lines in Gene Neighbors analysis from the Broad-Novartis Cancer Cell Line Encyclopedia (CCLE). The *x*-axis indicates cancer cell lines; *y*-axis indicates target probes and their corresponding gene names. *denotes known YAP target genes.

C Top 20 genes co-expressed with FOS across various cancer cell lines in Gene Neighbors analysis from the Broad-Novartis Cancer Cell Line Encyclopedia (CCLE). The *x*-axis indicates cancer cell lines; *y*-axis indicates target probes and their corresponding gene names. *denotes known YAP target genes.

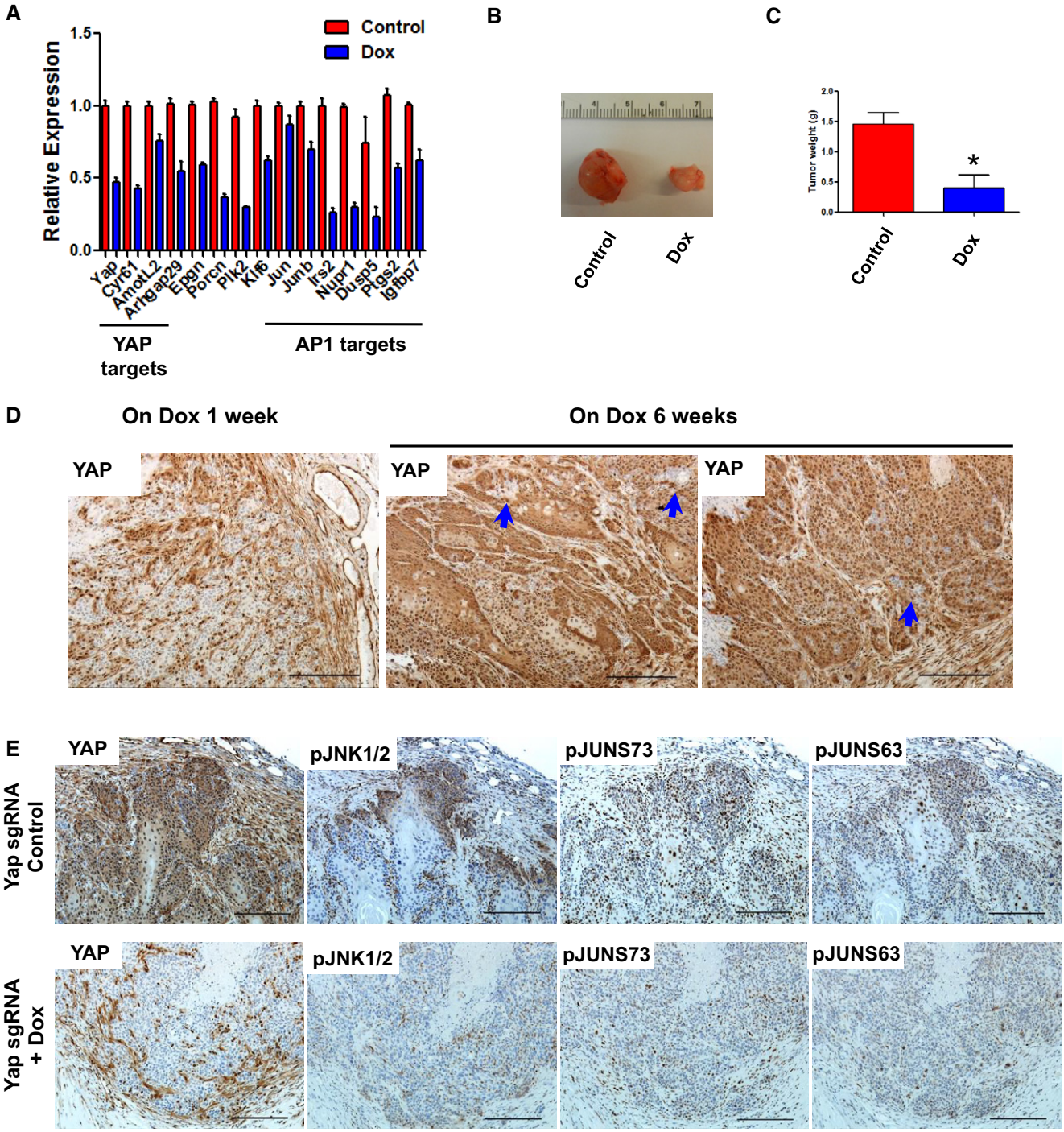


Figure EV5. YAP regulates JNK-JUN pathway in allograft and *in vitro* model of BCC.

A qPCR analysis of YAP and AP1 target genes in Dox-inducible *Yap* knockout (TetON-CRISPR-YapKO) ASZ cells. Error bars represent SEM. Total of three biological replicates were used per condition.

B Representative macroscopic images of TetON-CRISPR-YapKO ASZ allograft BCC tumors (Control versus Dox treatment for 6 weeks).

C Tumor weight quantification of Control versus Dox-treated TetON-CRISPR-YapKO ASZ allograft BCC tumors. Error bars represent SEM. The groups were compared using Student's *t*-test. $*P < 0.05$; $n = 3$ per group.

D YAP IHC in TetON-CRISPR-YapKO ASZ allograft tumors from mice receiving Dox for 1 week versus 6 weeks. Blue arrows indicate *Yap*-null clones. Scale bar is 100 μm.

E IHC analysis of YAP and JNK-JUN pathway activity in Control (*Yap*-wt) and Dox (*Yap*-null)-treated TetON-CRISPR-YapKO ASZ allograft BCC serial sections. Scale bar is 100 μm.

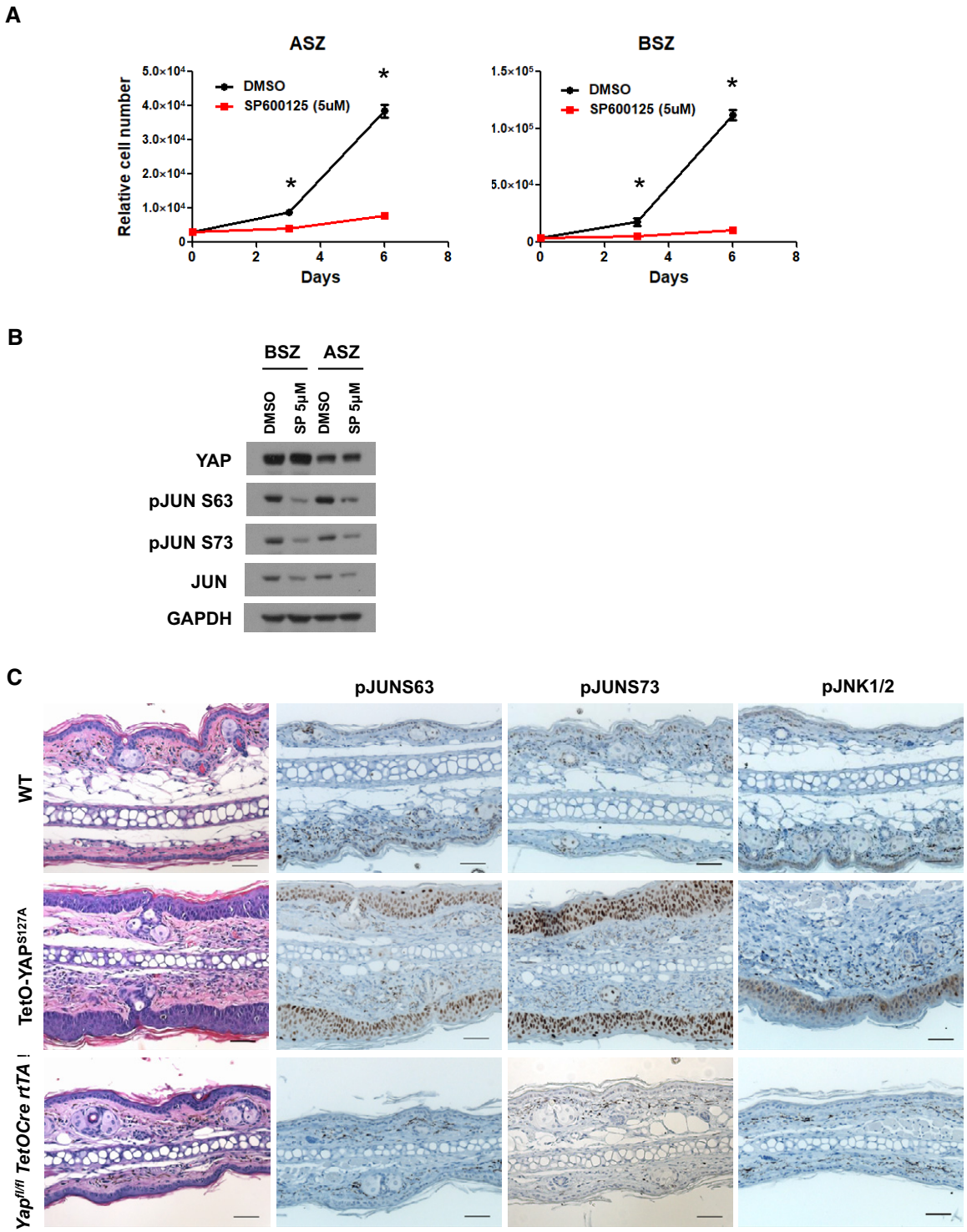


Figure EV6. YAP overexpression induces c-JUN activation and interfollicular epidermis thickening.

A JNK inhibitor (SP600125) blocks proliferation of BCC cell lines (ASZ and BSZ). The cells were treated *in vitro* with 5 μM SP600125 or DMSO over the course of 6 days, and growth was determined by cell counting. Total of three biological replicates were used per condition and time point. Error bars represent SEM. The groups were compared using ANOVA and Bonferroni post hoc test. *$P < 0.01$.

B Western blot analysis of YAP and JUN activity (pJUN S63 and pJUN S73) in ASZ and BSZ cells 16 h after JNK inhibition (SP600125 5 μM).

C YAP^{S127A} overexpression (*Col1*$^{TetO\text{-}YAPS127A}$ *R26*$^{LSL\text{-}rtTA/+}$ *K14Cre*) in adult epidermis upon administration of doxycycline to 8-week-old mice for 7 days. YAP^{S127A} induces interfollicular epidermis (IFE) thickening that closely resembles BCC. Representative H&E and IHC (pJUN S63, pJUN S73, pJNK1/2) images in WT, *TetO-YAP*^{S127A}, and *Yap*$^{fl/fl}$ *TetO-Cre rtTA* IFE. Scale bar is 50 μm.