

Supplemental Materials for

Targeting FAP α -expressing hepatic stellate cells overcomes resistance to anti-angiogenics in colorectal cancer liver metastasis models

Ming Qi[#], Shuran Fan[#], Maohua Huang[#], Jinghua Pan, Yong Li, Qun Miao, Wenyu Lyu, Xiaobo Li, Lijuan Deng, Shenghui Qiu, Tongzheng Liu, Weiqing Deng, Xiaodong Chu, Chang Jiang, Wenzhuo He, Liangping Xia, Yunlong Yang, Jian Hong, Qi Qi, Wenqian Yin, Xiangning Liu, Changzheng Shi, Minfeng Chen*, Wencai Ye*, Dongmei Zhang*

[#]These authors contributed equally to this work.

*Corresponding author

Dr. Dongmei Zhang, College of Pharmacy, Jinan University, 601 West Huangpu Avenue, Guangzhou, 510632, P. R. China. Phone: 86.208.522.2653; E-mail: dmzhang701@jnu.edu.cn.

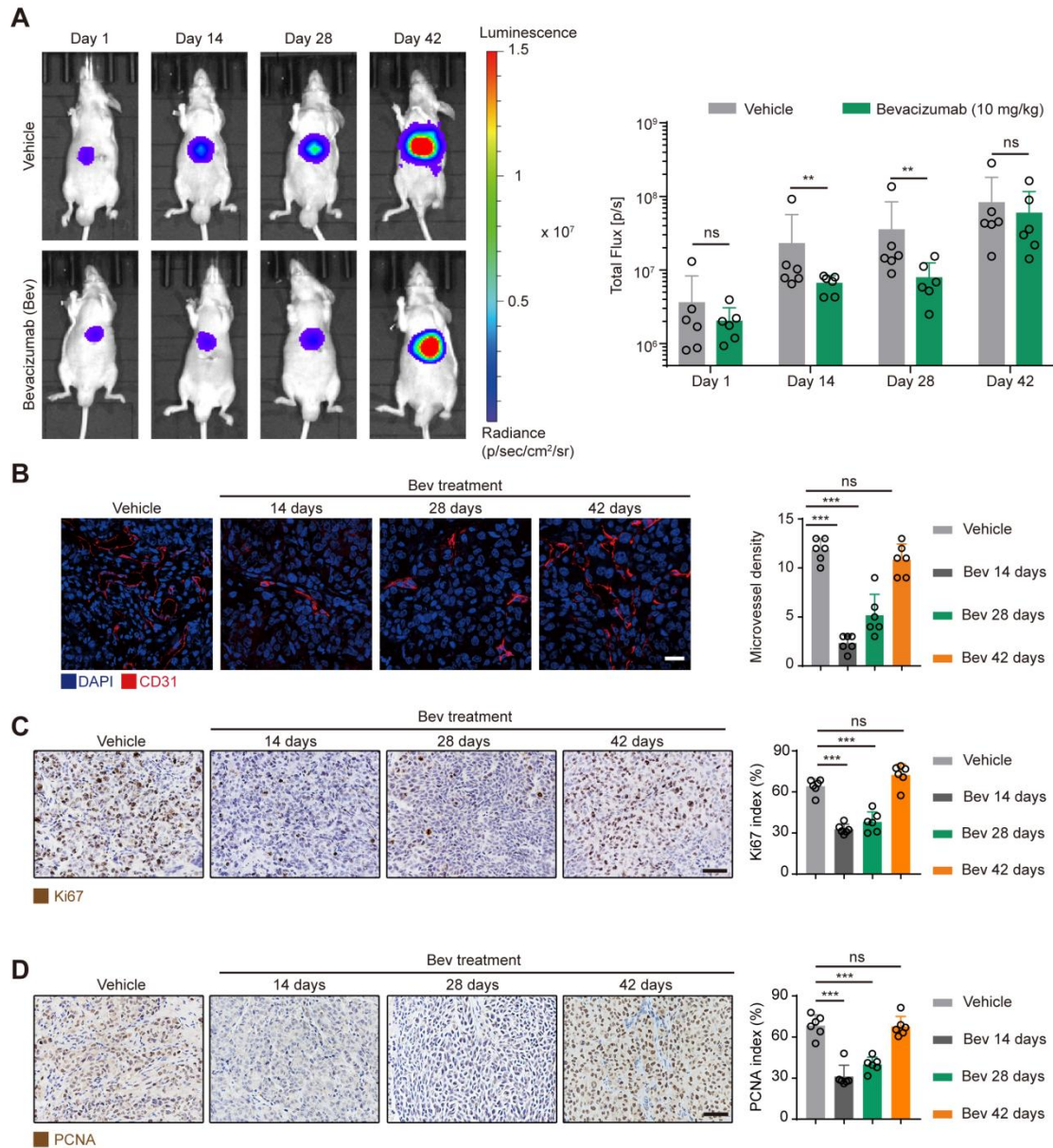
Dr. Wencai Ye, College of Pharmacy, Jinan University, 601 West Huangpu Avenue, Guangzhou, 510632, P. R. China. Phone: 86.208.522.0004; E-mail: chywc@aliyun.com.

Dr. Minfeng Chen, College of Pharmacy, Jinan University, 601 West Huangpu Avenue, Guangzhou, 510632, P. R. China. Phone: 86.208.522.8916; E-mail: minfengchen@jnu.edu.cn.

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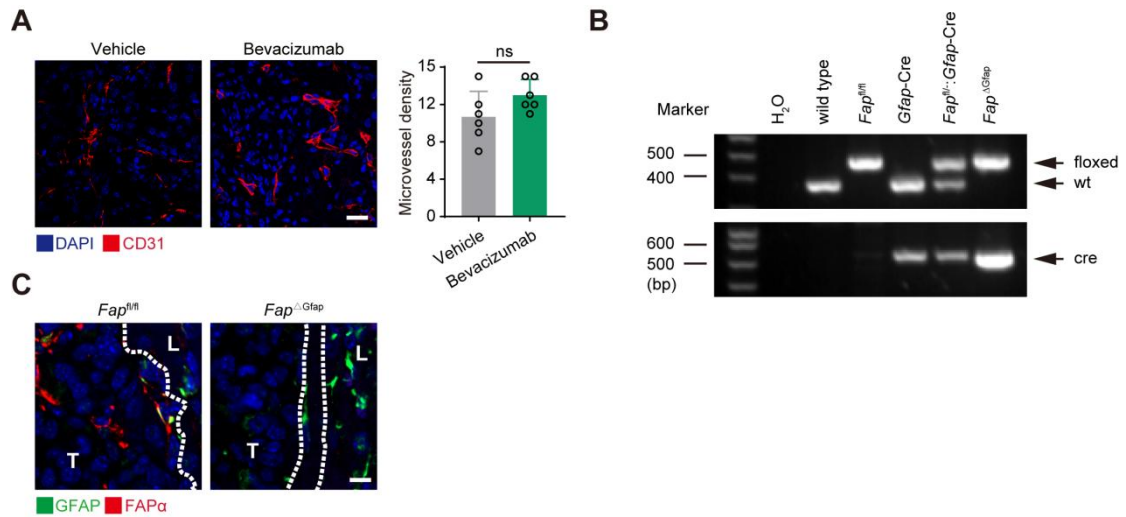
Supplemental Figure 1 to 16

Supplemental Table 1 to 10

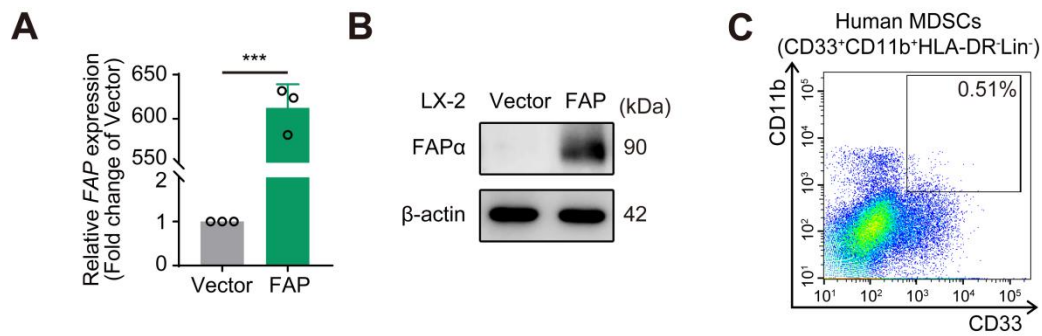


Supplemental Figure 1. Construction of the bevacizumab acquired resistant HCT116 CRCLM xenografts. (A) Representative images and quantification of bioluminescence signals in mice injected with HCT116-luc cells into the left main lobe of the liver ($n = 6$). (B) Immunofluorescence staining and quantification of CD31⁺ (red) tumor vessels ($n = 6$). Scale bar, 20 μm . (C) Immunohistochemical staining and quantification of Ki67 in tumor tissues ($n = 6$). Scale bar, 50 μm . (D) Immunohistochemical staining and quantification of PCNA in tumor tissues ($n = 6$).

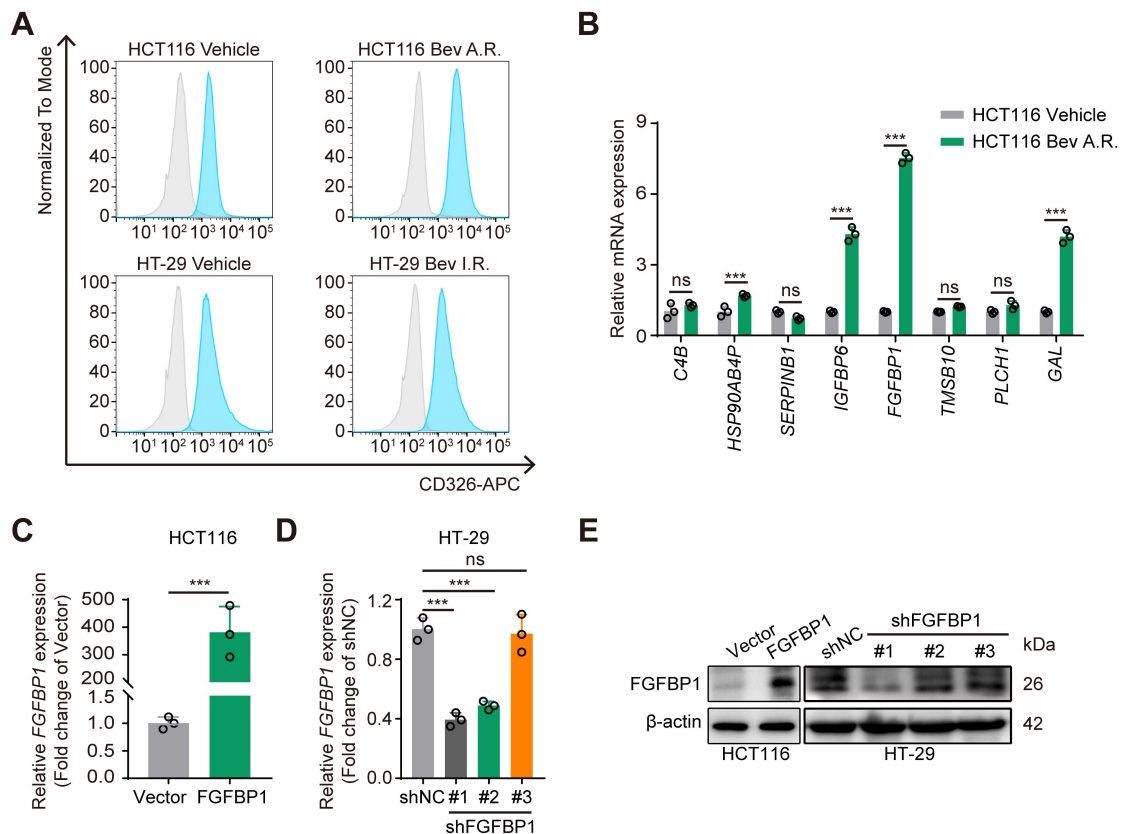
Scale bar, 50 μm . Data are presented as mean \pm SEM. ns, no significance; $**P < 0.01$, $***P < 0.001$ (2-tailed unpaired t test in A; 1-way ANOVA with Tukey's post hoc comparison in B-D).



Supplemental Figure 2. Characteristics of the HSC-specific conditional *Fap*-knockout mice and the MC38 CRCLM allografts. (A) Immunofluorescence staining of CD31⁺ tumor vessels (red) in MC38 CRCLM allografts. Quantification of microvessel density is shown (n = 6). Scale bar, 20 μm . (B) Genotyping of the transgenic mice. The genomic DNA derived from the indicated mice were analyzed by PCR assay, and the DNA fragments were separated on 2% agarose gels (n = 6). (C) Immunofluorescence staining of FAP α (red) in the GFAP⁺ HSCs (green) in MC38 CRCLM allografts (n = 6). Scale bar, 10 μm . Data are presented as mean \pm SEM. ns, no significance.

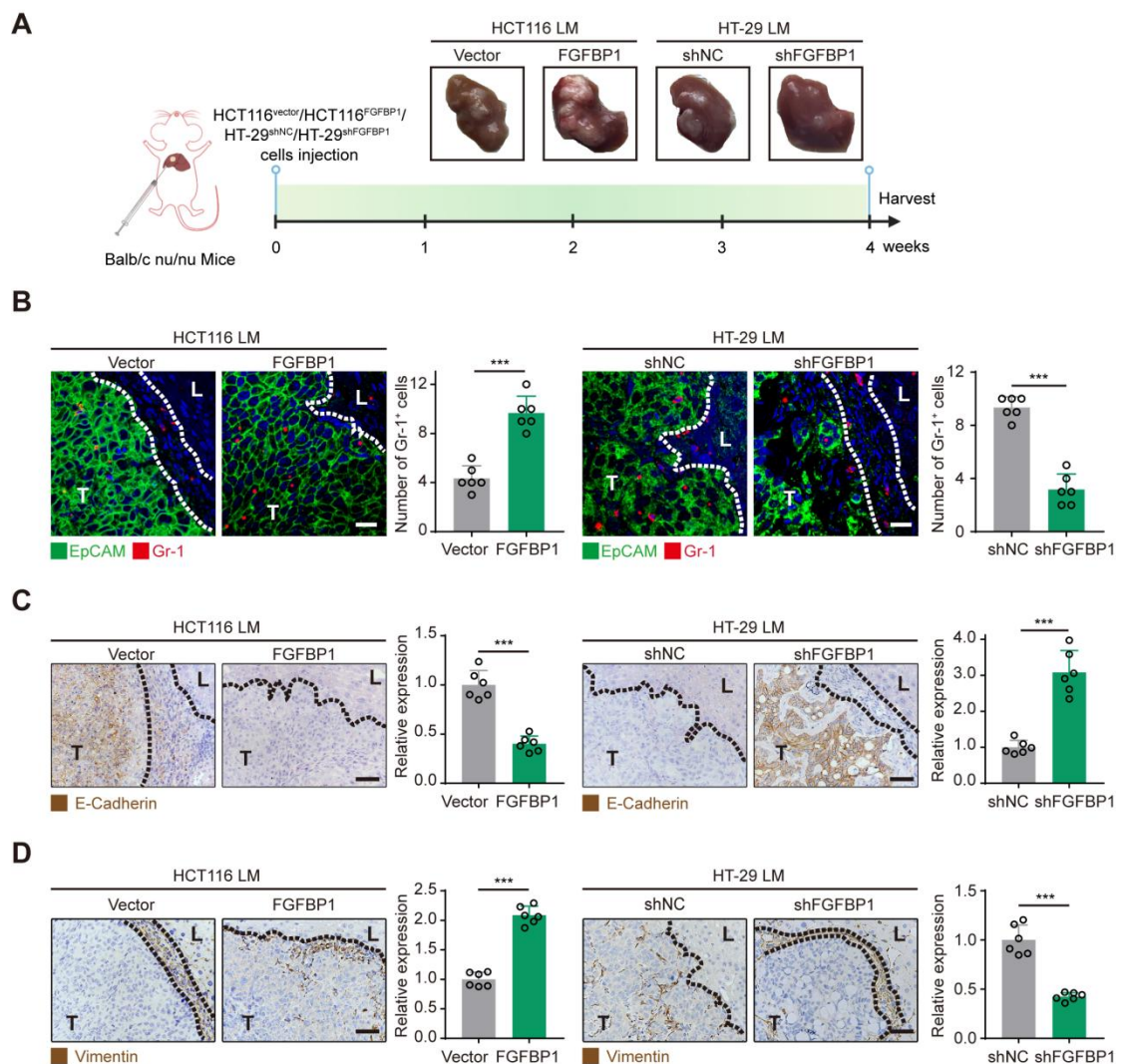


Supplemental Figure 3. FAP α ⁺ HSCs facilitate vessel co-option via promoting recruitment of MDSCs and tumor cell EMT. (A) RT-qPCR analysis of the levels of *FAP* in LX-2 cells (n = 3). (B) Western blotting analysis of the expression of FAP α in LX-2 cells. (C) FCM analysis of MDSCs isolated from human CRC tumor samples. Data are presented as mean \pm SEM. ****P* < 0.001 (2-tailed unpaired *t* test).



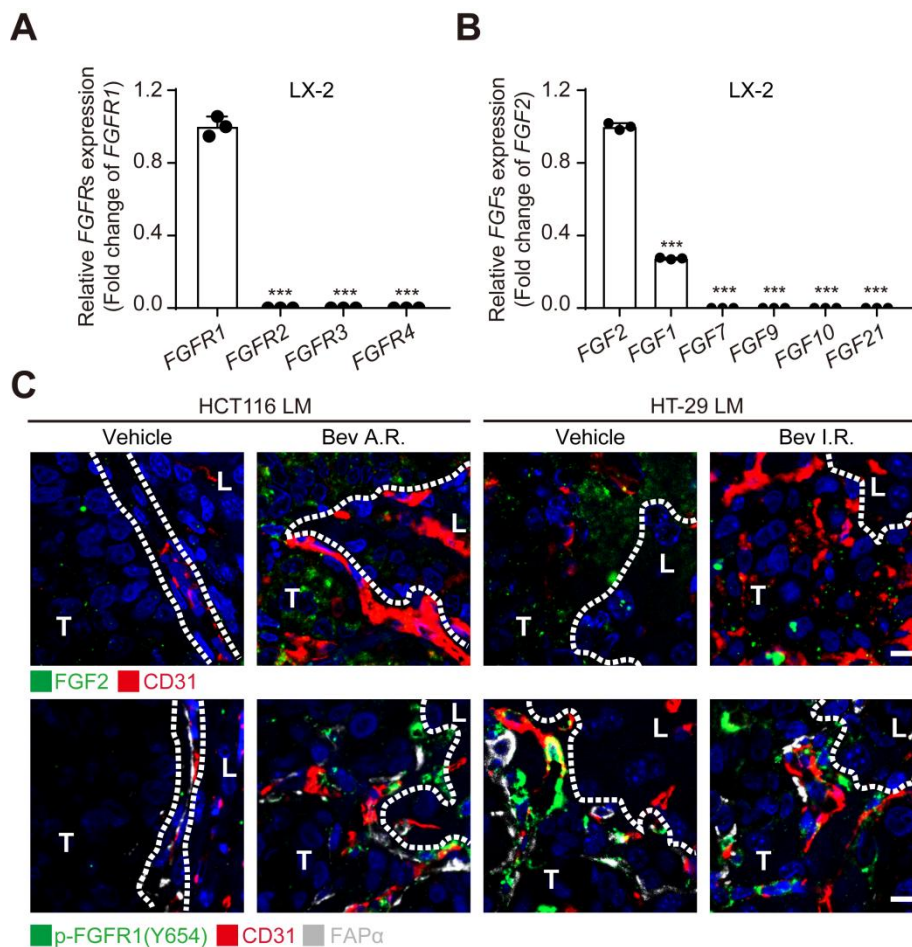
Supplemental Figure 4. Evaluation of the expression of FGFBP1 in HCT116 or HT-29 cells. (A) FCM analysis of the primary tumor cells isolated from

bevacizumab-sensitive or -resistant CRCLM xenografts. (B) RT-qPCR analysis of the levels of genes indicated by proteomic assay in HCT116 cells (n = 3). (C) RT-qPCR analysis of the overexpression of *FGFBP1* in HCT116 cells (n = 3). (D) RT-qPCR analysis of the knockdown of *FGFBP1* in HT-29 cells (n = 3). (E) Western blotting analysis of FGFBP1 in HCT116 and HT-29 cells after the indicated transfections. Data are presented as mean \pm SEM. ns, no significance, *** $P < 0.001$ (2-tailed unpaired *t* test in B, C; 1-way ANOVA with Tukey's post hoc comparison in D).

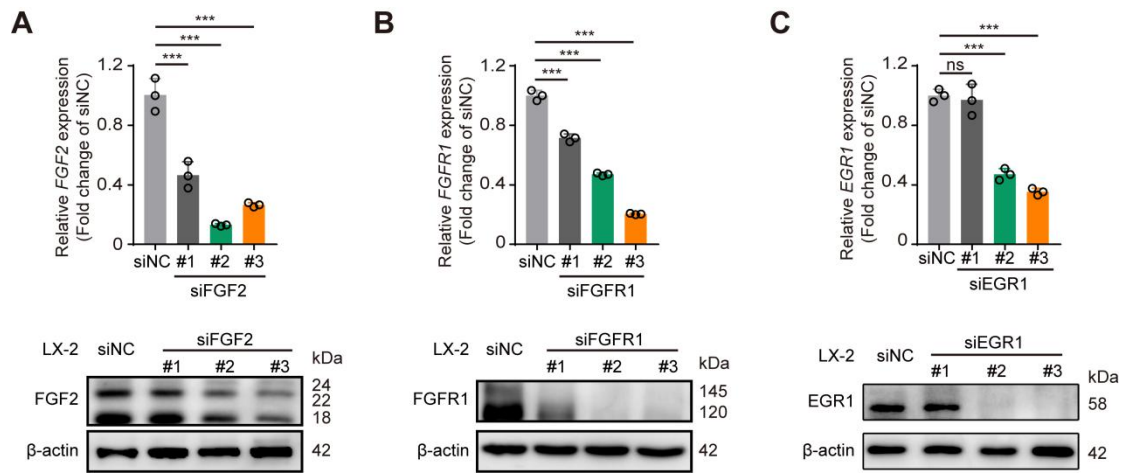


Supplemental Figure 5. Tumor-derived FGFBP1 promotes of MDSC recruitment and tumor cell EMT in CRCLM xenografts. (A) Schematic showing

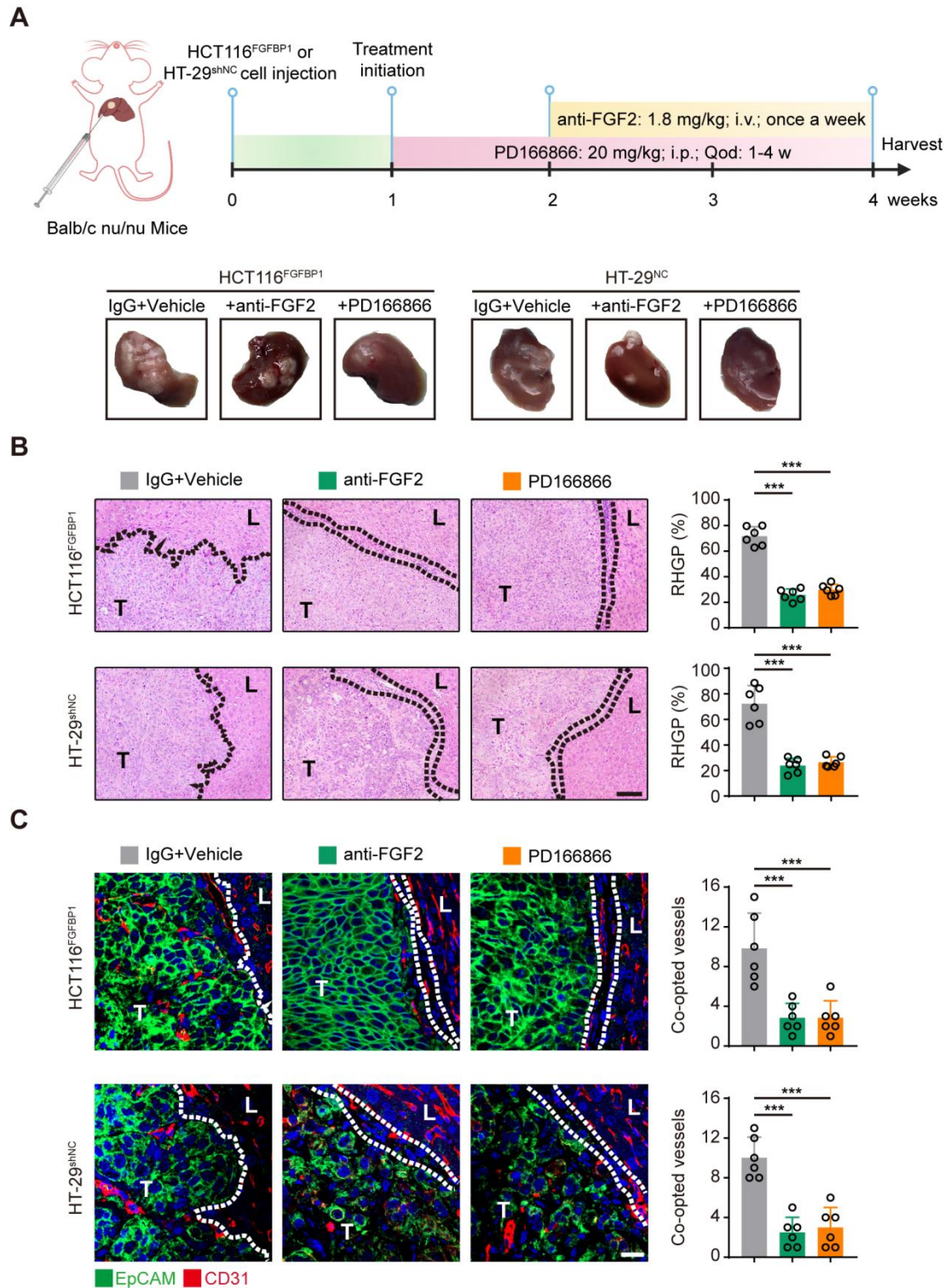
the establishment of the FGFBP1-knockdown or -overexpression CRCLM xenografts. Tumors were harvested and photographed at the end of experiments (n = 6). (B) Immunofluorescence staining of EpCAM⁺ (green) tumor cells and Gr-1⁺ MDSCs (red) in the tumor-liver interface of CRCLM xenografts. Scale bar, 50 μm. Quantification of Gr-1⁺ MDSCs is shown (n = 6). (C) Immunohistochemical staining and quantification of E-cadherin in the tumor-liver interface of CRCLM xenografts (n = 6). Scale bar, 50 μm. (D) Immunohistochemical staining and quantification of vimentin in the tumor-liver interface of CRCLM xenografts (n = 6). Scale bar, 50 μm. Dotted lines indicate the tumor-liver interface. LM, liver metastases; T, Tumor; L, Liver. Data are presented as mean ± SEM. ****P* < 0.001 (2-tailed unpaired *t* test).



Supplemental Figure 6. FGF2 and FGFR1 are highly expressed in HSCs. (A) RT-qPCR assay analysis of the levels of *FGFRs* in LX-2 cells (n = 3). (B) RT-qPCR assay analysis of the levels of *FGFs* in LX-2 cells (n = 3). (C) Immunofluorescence staining of FGF2⁺ (green), p-FGFR1⁺ (green), or FAP α ⁺ (gray) HSCs, and CD31⁺ sinusoidal blood vessels (red) in the tumor-liver interface of CRCLM xenografts (n = 6). Scale bar, 10 μ m. Data are presented as mean \pm SEM. ****P* < 0.001 compared to *FGFR1* or *FGF1* group (1-way ANOVA with Tukey's post hoc comparison).

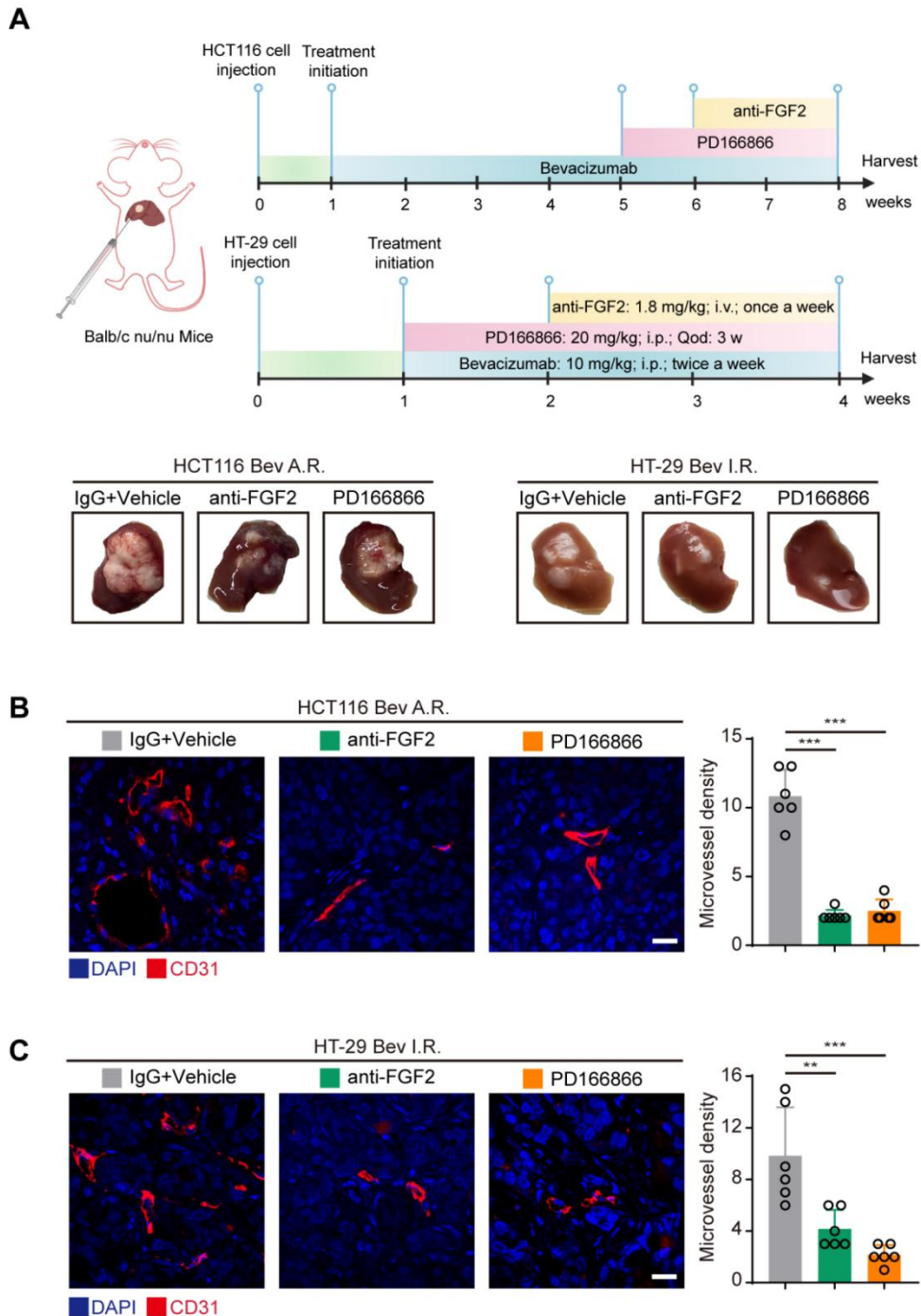


Supplemental Figure 7. Validation of knockdown efficiency of FGF2, FGFR1, and EGR1 in HSCs. (A-C) RT-qPCR and Western blotting analysis of the knockdown of FGF2 (A), FGFR1 (B), and EGR1 (C) in LX-2 cells (n = 3). Data are presented as mean \pm SEM. ns, no significance, ****P* < 0.001 (1-way ANOVA with Tukey's post hoc comparison).



Supplemental Figure 8. Evaluation of the efficacy of FGF2 neutralizing antibody or PD166866 in FGFBP1-overexpressing CRCLM xenografts. (A) Experimental design of the FGF2 neutralizing antibody and PD-166866 (an FGFR1 inhibitor) treatments in HCT116 or HT-29 CRCLM xenografts (n = 6). (B) H&E staining of the

tumor-liver interface of CRCLM xenografts. Scale bar: 100 μm . Quantification of RHGP is shown ($n = 6$). (C) Immunofluorescence staining of the EpCAM⁺ tumor cells (green) infiltrated into the liver parenchyma and hijacked the CD31⁺ sinusoidal blood vessels (red) in the tumor-liver interface of CRCLM xenografts. Scale bar: 20 μm . Quantification of the co-opted sinusoidal blood vessels is shown ($n = 6$). Data are presented as mean \pm SEM. *** $P < 0.001$ (1-way ANOVA with Tukey's post hoc comparison).

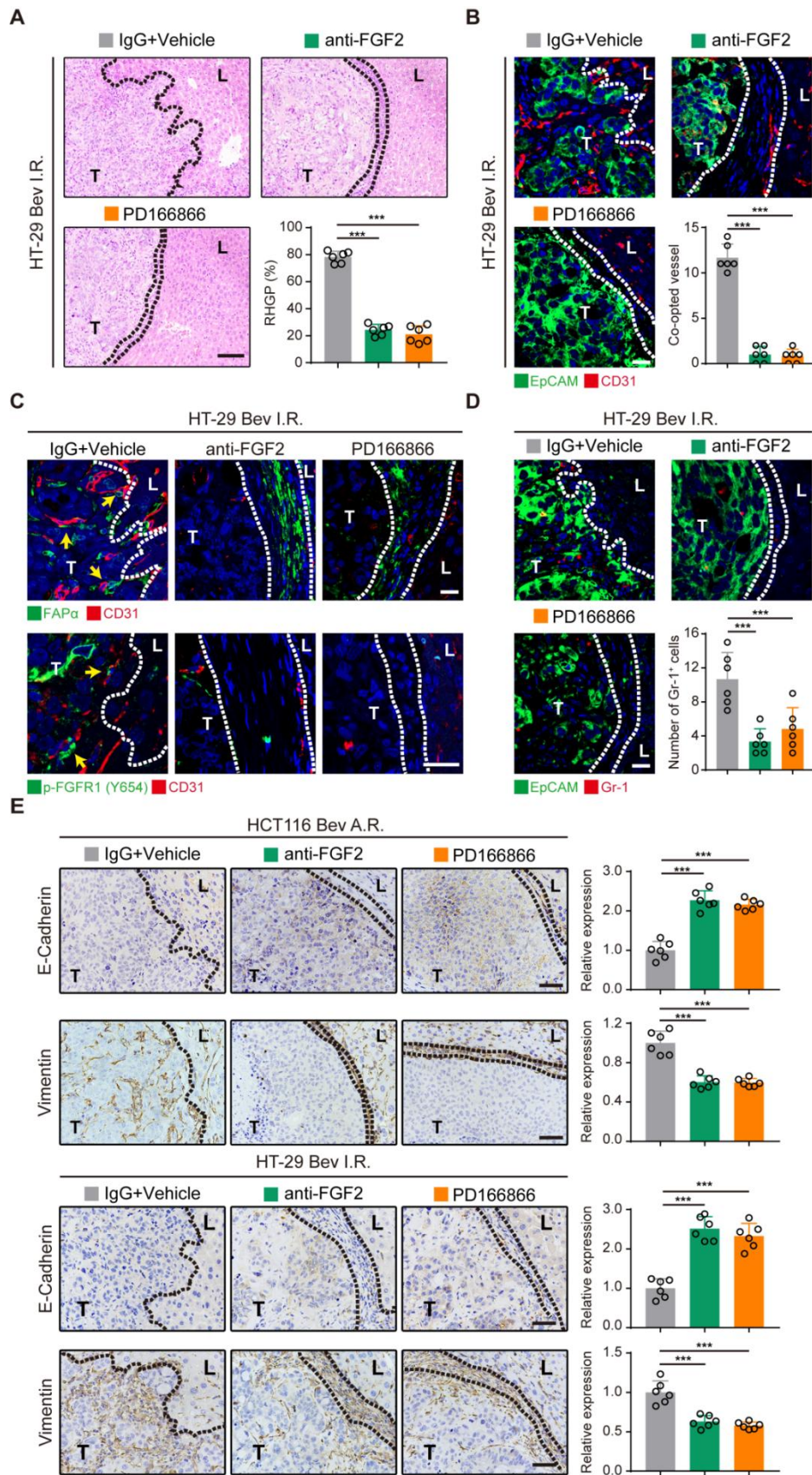


Supplemental Figure 9. Evaluation of the efficacy of FGF2 neutralizing antibody or PD166866 in bevacizumab-resistant CRCLM xenografts. (A) Therapeutic schedule for HCT116 and HT-29 xenografts treated with bevacizumab with or without FGF2 neutralizing antibody or PD166866 (n = 6). (B) Immunofluorescence staining and quantification of CD31⁺ tumor vessels (red) in HCT116 CRCLM xenografts (n = 6). Scale bar, 20 μ m. (C) Immunofluorescence staining and

quantification of CD31⁺ tumor vessels (red) in HT-29 CRCLM xenografts (n = 6).

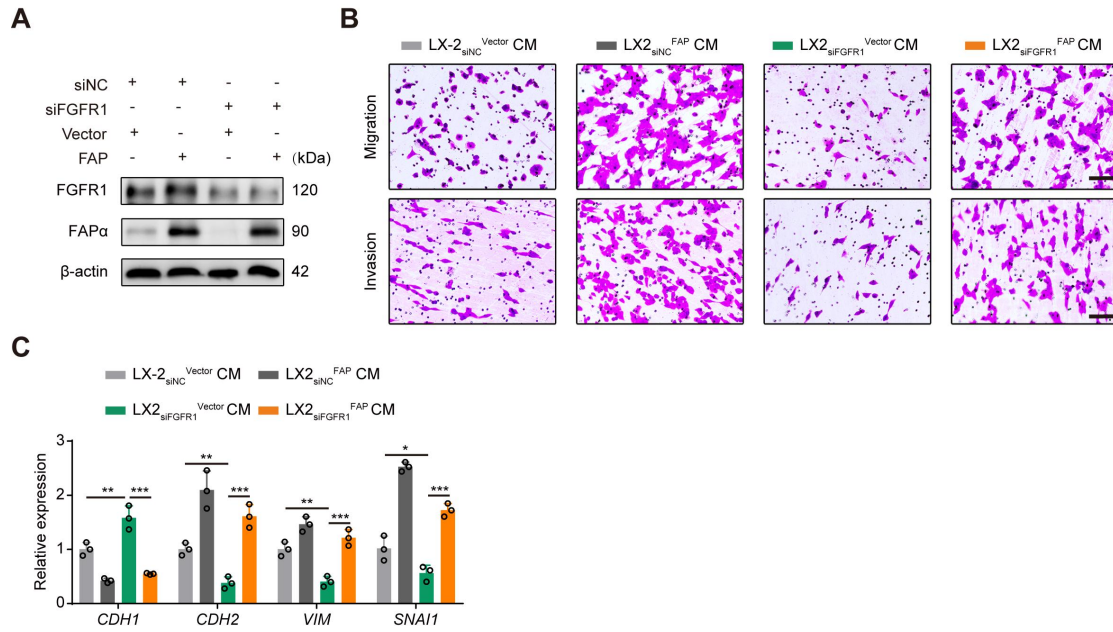
Scale bar, 20 μm . Data are presented as mean \pm SEM. ** $P < 0.01$, *** $P < 0.001$

(1-way ANOVA with Tukey's post hoc comparison).

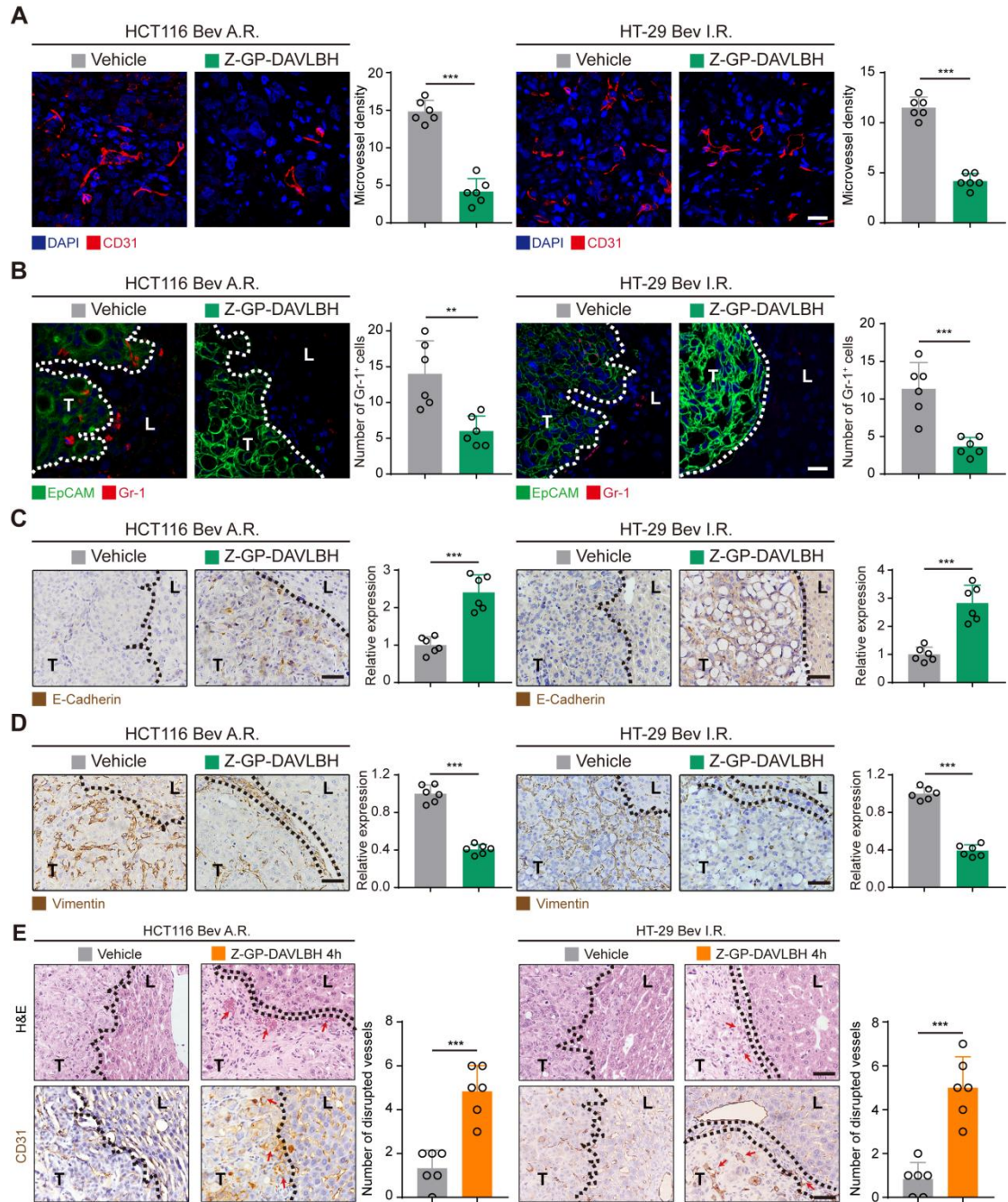


Supplemental Figure 10. Blockade of FGF2-FGFR1 signaling pathway in HSCs attenuates the bevacizumab-induced vessel co-option. (A) H&E staining of the

tumor-liver interface of HT-29 CRCLM xenografts. Scale bar: 100 μm . Quantification of RHGP is shown ($n = 6$). (B) Immunofluorescence staining of the EpCAM⁺ tumor cells (green) infiltrated into the liver parenchyma and hijacked the CD31⁺ sinusoidal blood vessels (red) in the tumor-liver interface of HT-29 CRCLM xenografts. Scale bar: 20 μm . Quantification of the co-opted sinusoidal blood vessels is shown ($n = 6$). (C) Immunofluorescence staining of the FAP α (green) and p-FGFR1⁺ in HSCs attached on the CD31⁺ sinusoidal blood vessels (red) in the tumor-liver interface of HT-29 CRCLM xenografts. Scale bar, 20 μm . Yellow arrows indicate the FAP α ⁺ or p-FGFR1⁺ HSCs. (D) Immunofluorescence staining of the EpCAM⁺ (green) tumor cells and Gr-1⁺ MDSCs (red) in the tumor-liver interface of HT-29 CRCLM xenografts. Scale bar, 20 μm . Quantification of Gr-1⁺ MDSCs is shown ($n = 6$). (E) Immunohistochemical staining and quantification of E-cadherin and vimentin in the tumor-liver interface of HCT116 and HT-29 CRCLM xenografts ($n = 6$). Scale bar, 50 μm . Dotted lines indicate the tumor-liver interface. Bev I.R., bevacizumab intrinsic resistance. T, Tumor. L, Liver. Data are presented as mean \pm SEM. *** $P < 0.001$ (1-way ANOVA with Tukey's post hoc comparison).

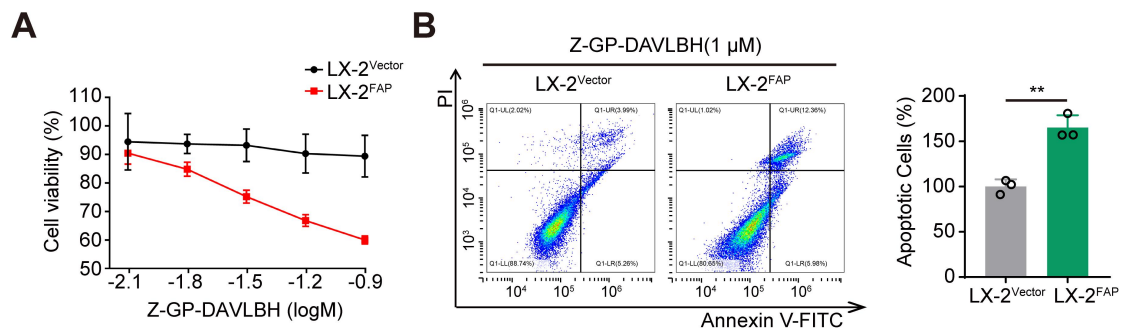


Supplemental Figure 11. FGFR1-FAP α axis is essential for tumor cell EMT. (A) Western blotting analysis of FGFR1 and FAP α in LX-2 cells with FGFR1-knockdown and/or FAP α -overexpression. (B) Transwell assays of the migration and invasion of HCT116 cells treated with the conditioned medium from LX-2 cells (n = 3). (C) RT-qPCR analysis of *CDH1*, *CDH2*, *SNAIL1*, and *VIM* in HCT116 cells treated with the conditioned medium from LX-2 cells (n = 3). Data are presented as mean \pm SEM. ns, no significance; * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ (1-way ANOVA with Tukey's post hoc comparison). CM: conditioned medium.

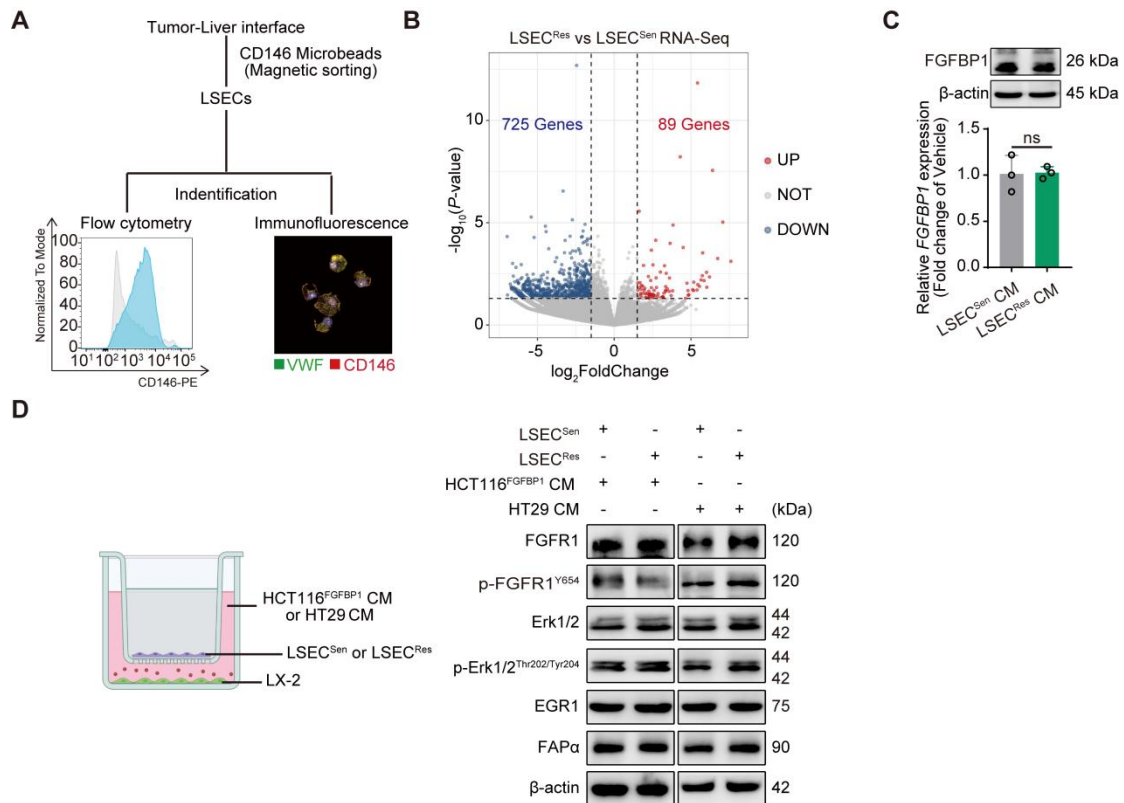


Supplemental Figure 12. Z-GP-DAVLBH inhibits the recruitment of MDSCs and tumor cell EMT. (A) Immunofluorescence staining and quantification of CD31⁺ tumor vessels (red) in HCT116 and HT-29 CRCLM xenografts (n = 6). Scale bar, 20 μ m. (B) Immunofluorescence staining of Gr-1⁺ MDSCs (red) and EpCAM⁺ tumor cells (green) in the liver-tumor interface of CRCLM xenografts. Scale bar, 20 μ m. Quantification of Gr-1⁺ MDSCs is shown (n = 6). (C) Immunohistochemical staining and quantification of E-cadherin in the liver-tumor interface of CRCLM xenografts (n

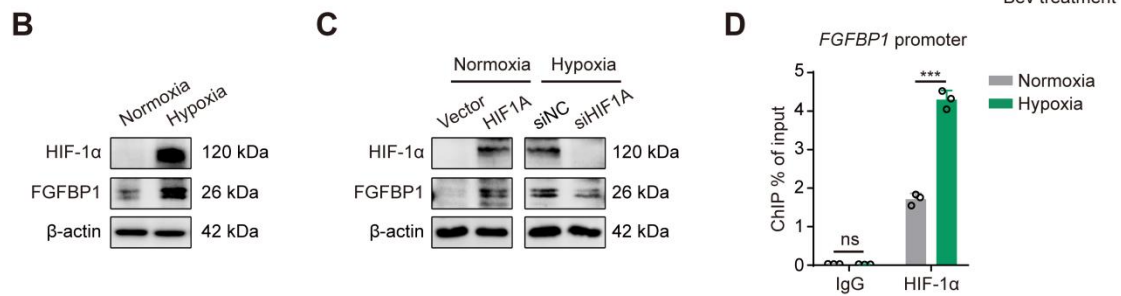
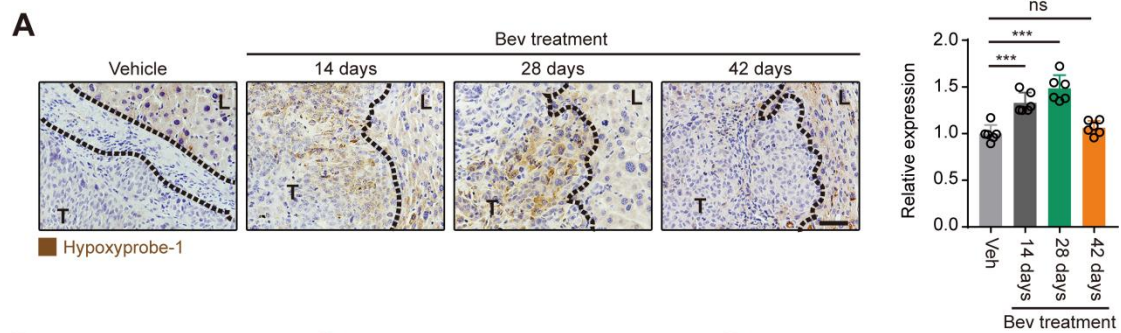
= 6). Scale bar, 50 μm . (D) Immunohistochemical staining and quantification of vimentin in the tumor-liver interface of CRCLM xenografts ($n = 6$). Scale bar, 50 μm . (E) H&E and immunohistochemical staining showed that Z-GP-DAVLBH induced vessel disruption in the tumor-liver interface of CRCLM xenografts. Red arrows indicate the “hole-like” disruptions in the tumor vessels. Scale bar, 50 μm . Quantification of the disrupted vessels is shown ($n = 6$). T, Tumor. L, Liver. Data are presented as mean \pm SEM. $**P < 0.01$, $***P < 0.001$ (2-tailed unpaired t test).



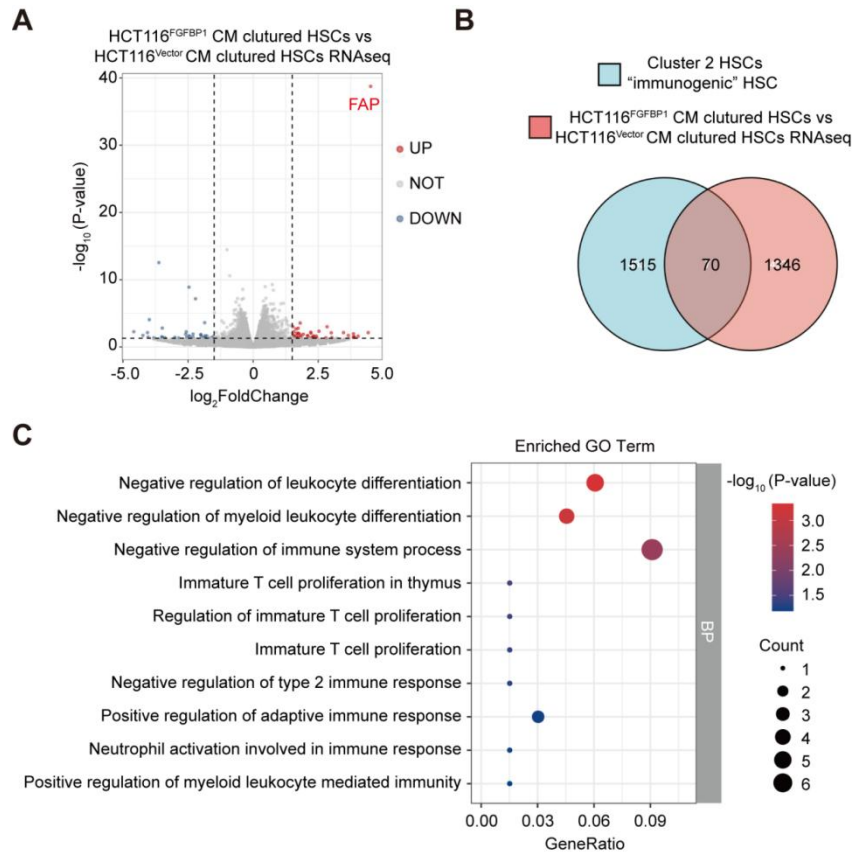
Supplemental Figure 13. Z-GP-DAVLBH selectively induces apoptosis in FAP α ⁺ HSCs. (A) CCK-8 assay analysis of the effect of Z-GP-DAVLBH on the cell viability of LX-2 cells ($n = 3$). (B) FCM analysis of the apoptotic LX-2 cells after treatment with Z-GP-DAVLBH (1 μM) for 4 h ($n = 3$). Data are presented as mean \pm SEM. $**P < 0.01$ (2-tailed unpaired t test).



Supplemental Figure 14. Effects of liver sinusoidal endothelial cells on LX2 cells and HCT116 cells. (A) Schematic diagram of the isolation and identification of primary LSECs from the liver-tumor interface of HCT116 CRCLM xenografts. (B) Volcano plot depicting the differentially expressed genes in LSECs obtained from bevacizumab-sensitive and -resistant HCT116 CRCLM xenografts ($\log_2\text{FoldChange} > 1.5$, $P\text{-value} < 0.05$; $n = 3$). Res, bevacizumab-resistant. Sen, bevacizumab-sensitive. (C) RT-qPCR and Western blotting analysis of FGFBP1 in HCT116 cells treated with the conditioned medium from LSECs ($n = 3$). (D) Western blotting analysis of FGFR1, p-FGFR1, ERK1/2, p-ERK1/2, EGR1, and FAP α in LX-2 cells cocultured with LSECs and treated with the conditioned medium from HCT116 or HT-29 cells. Data are presented as mean \pm SEM. ns, no significance (2-tailed unpaired t test). CM: conditioned medium.



Supplemental Figure 15. Hypoxia is responsible for the expression of FGFBP1 in tumor cells. (A) Immunohistochemical staining and quantification of hypoxyprobe-1 in bevacizumab-treated HCT116 CRCLM xenografts (n = 6). Scale bar, 50 μ m. (B) Western blotting analysis of HIF-1 α and FGFBP1 in normoxic or hypoxic HCT116 cells. (C) Western blotting analysis of HIF-1 α and FGFBP1 in normoxic or hypoxic HCT116 cells with HIF1 α -overexpression or -knockdown. (D) ChIP-qPCR analysis of the binding of HIF-1 α to the *FGFBP1* promoter (n = 3). Data are presented as mean \pm SEM. ns, no significance; *** P < 0.001 (1-way ANOVA with Tukey's post hoc comparison in A; 2-tailed unpaired t test in D).



Supplemental Figure 16. HSCs may partially transform into an "immunogenic" phenotype during vessel co-option. (A) Volcano Plot depicting differentially expressed genes in LX-2 cells primed with the conditioned medium from HCT116 cells ($\log_2\text{FoldChange} > 1.5$, $P\text{-value} < 0.05$; $n = 3$). (B) Venn diagram illustrating the overlapping genes between the upregulated genes in HCT116 cell conditioned medium-treated LX-2 cells analyzed by RNA-seq and the differential expression genes (DEG) in cluster 4 HSCs ("immunogenic" HSCs) analyzed by scRNA-seq (GSE171904). (C) Gene ontology (GO) enrichment analysis of the 70 overlapping genes in (B).

Supplemental Table 1. Characteristics of 45 patients (n = 53 lesions) treated preoperatively with Chemo or Chemo+Bev prior to liver resection at Guangzhou Overseas Chinese Hospital (Detailed patients' information in Figure 7A).

Demographics	
Gender, number of patients (%)	
Male	32 (71.1)
Female	13 (28.9)
Age, median (range)	56 (27 – 75)
Primary tumor	
Site of primary tumor, number of patients (%)	
Rectum	24 (53.3)
Recto–sigmoid	11 (24.5)
Colon	10 (22.2)
Lymph node status, number of patients (%)	
Positive	28 (62.2)
Negative	17 (37.8)
Histological grade, number of patients (%)	
High grade	1 (2.2)
Moderate grade	42 (93.3)
Low grade	2 (4.5)
Adjuvant Bev therapy, number of patients (%)	
Yes	31 (68.9)
No	14 (31.1)
Liver metastasis	
No. of liver lesions at presentation, number of patients (%)	
Solitary lesion	40 (88.9)
Multiple lesions	5 (11.1)
Preoperative therapy administered, number of patients (%)	
CAPOX + bevacizumab	4 (8.9)
FOLFOX + bevacizumab	14 (31.1)
FOLFIRI + bevacizumab	9 (20.0)
FOLFOXIRI+ bevacizumab	3 (6.7)
Oxaliplatin+Capecitabine+Bevacizumab	1 (2.2)
FOLFOX	7 (15.5)
FOLFIRI	3 (6.7)
CAPOX	4 (8.9)

Footnote: CAPOX, capecitabine and oxaliplatin; FOLFOX, infusional 5-fluorouracil and oxaliplatin; FOLFIRI, infusional 5-fluorouracil and irinotecan; FOLFOXIRI, infusional 5-fluorouracil, oxaliplatin and irinotecan.

Supplemental Table 2. Characteristics of 66 patients (n = 82 lesions) treated preoperatively with Chemo or Chemo+Bev prior to liver resection at Guangzhou Overseas Chinese Hospital (Detailed patients' information in Figure 7, B-E).

Demographics	
Gender, number of patients (%)	
Male	45 (68.2)
Female	21 (31.8)
Age, median (range)	56 (27 – 75)
Primary tumor	
Site of primary tumor, number of patients (%)	
Rectum	28 (42.4)
Recto–sigmoid	21 (31.8)
Colon	16(24.3)
Cecum	1(1.5)
Lymph node status, number of patients (%)	
Positive	41 (62.1)
Negative	25 (37.9)
Histological grade, number of patients (%)	
High grade	3 (4.5)
Moderate grade	59 (89.4)
Low grade	4 (6.1)
Adjuvant Bev therapy, number of patients (%)	
Yes	37 (56.1)
No	29 (43.9)
Liver metastasis	
No. of liver lesions at presentation, number of patients (%)	
Solitary lesion	54 (81.8)
Multiple lesions	12 (18.2)
Preoperative therapy administered, number of patients (%)	
CAPOX + bevacizumab	11 (16.7)
FOLFOX + bevacizumab	15 (22.7)
FOLFIRI + bevacizumab	8 (12.1)
FOLFOXIRI+ bevacizumab	3 (4.5)
CAPOX	10 (15.2)
FOLFOX	12 (18.2)
FOLFIRI	2(3.0)
FOLFOXIRI	5 (7.6)

Footnote: CAPOX, capecitabine and oxaliplatin; FOLFOX, infusional 5-fluorouracil and oxaliplatin; FOLFIRI, infusional 5-fluorouracil and irinotecan; FOLFOXIRI, infusional 5-fluorouracil, oxaliplatin and irinotecan.

Supplemental Table 3. Characteristics of 34 patients (n = 42 lesions) treated preoperatively with Chemo or Chemo+Bev prior to liver resection at Guangzhou Overseas Chinese Hospital (Detailed patients' information in Figure 7F).

Demographics	
Gender, number of patients (%)	
Male	22 (64.7)
Female	12 (35.3)
Age, median (range)	55 (28 – 73)
Primary tumor	
Site of primary tumor, number of patients (%)	
Rectum	11 (32.3)
Recto–sigmoid	14 (41.2)
Colon	8(23.5)
Cecum	1 (3.0)
Lymph node status, number of patients (%)	
Positive	21 (61.8)
Negative	13 (38.2)
Histological grade, number of patients (%)	
High grade	2 (5.9)
Moderate grade	30 (88.2)
Low grade	2 (5.9)
Adjuvant Bev therapy, number of patients (%)	
Yes	18 (52.9)
No	16 (47.1)
Liver metastasis	
No. of liver lesions at presentation, number of patients (%)	
Solitary lesion	28 (82.4)
Multiple lesions	6 (17.6)
Preoperative therapy administered, number of patients (%)	
FOLFOX + bevacizumab	7 (20.6)
FOLFIRI + bevacizumab	3 (8.8)
FOLFOXIRI+ bevacizumab	1 (3.0)
CAPOX+ bevacizumab	6 (17.6)
Oxaliplatin+Capecitabine+Bevacizumab	1 (3.0)
FOLFOX	6 (17.6)
FOLFOXIRI	3 (8.8)
CAPOX	7 (20.6)

Footnote: CAPOX, capecitabine and oxaliplatin; FOLFOX, infusional 5-fluorouracil and oxaliplatin; FOLFIRI, infusional 5-fluorouracil and irinotecan; FOLFOXIRI, infusional 5-fluorouracil, oxaliplatin and irinotecan.

Supplemental Table 4. List of primers sequences for PCR analysis of genomic DNA from tail snips.

Primer name	Sequence	Band Size
T004857-F1A	GGGCAGTCTGGTACTTCCAAGCT	WT:0bp
T004857-R1A	GGGCAGUAUAAACUUGGAUTT	Targeted:515bp
T052266-F1	CATCGCATTGTCTGAGTAGGTG	WT:365bp
T052266-R1	CTCCAGCAAGGCTGCACAAT	Targeted:467bp

Supplemental Table 5. List of shRNA sequences for cell transfection.

Gene name	Target sequence
<i>FGFBP1</i> -shRNA-1	GAGGGCATCTCTCTCAAGGTT
<i>FGFBP1</i> -shRNA-2	AAGCTAGTCAGCTCCACTCTA
<i>FGFBP1</i> -shRNA-3	CAGGGAGCACATCAAAGGCAA

Supplemental Table 6. List of siRNA sequences for cell transfection.

Gene name	Sense sequence (5' to 3')	Antisense sequence (5' to 3')
<i>FGF2</i> -Homo-638	CCUCACAUCAAGCUACAATT	UUGUAGCUUGAUGUGAGGGTT
<i>FGF2</i> -Homo-693	GGAGUGUGUGCUAACCGUUTT	AACGGUUAGCACACACUCCTT
<i>FGF2</i> -Homo-858	GGGCAGUAUAAACUUGGAUTT	AUCCAAGUUUUAUCUGCCCTT
<i>FGFR1</i> -Homo-1265	GCAGUGACACCACCUACUUTT	AAGUAGGUGGUGUCACUGCTT
<i>FGFR1</i> -Homo-2598	GCAGGAUGGUCCCUUGUAUTT	AUACAAGGGACCAUCCUGCTT
<i>FGFR1</i> -Homo-3116	GCACCAACGAGCUGUACAUTT	AUGUACAGCUCGUUGGUGCTT
<i>EGR1</i> -Homo-1354	CCCGGUUACUACCUCUUAUTT	AUAAGAGGUAGUAACCGGGTT
<i>EGR1</i> -Homo-1264	GGACAAGAAAGCAGACAAATT	UUUGUCUGCUUUCUUGUCCTT
<i>EGR1</i> -Homo-324	CUCUGAACAAACGAGAAGGUTT	ACCUUCUCGUUGUUCAGAGTT
<i>HIF1A</i> -Homo-964	GCUGAUUUGUGAACCCAUUTT	AAUGGGUUCACAAAUCAGCTT

Supplemental Table 7. List of antibodies for immunohistochemistry and immunofluorescence.

Antibodies	Supplier; catalogue number
Goat anti-CD31	R&D System; AF3628
Rabbit anti- CD31	Servicebio; GB14033
Rabbit anti-EpCAM	Abcam; ab71916
Sheep anti-FAP α	R&D System; AF3715
Rabbit anti- FAP α	Affinity; AF5344
Mouse anti-Gr-1	R&D System; MAB1037

Rabbit anti-CD8	Abcam; ab217344
Mouse anti- α -SMA	Servicebio; GB13044
Rabbit anti-GFAP	Servicebio; GB11096
Rabbit anti-CK18	Servicebio; GB11232
Mouse anti-E-Cadherin	Cell Signal Technology; 14472S
Mouse anti-Vimentin	Abcam; ab8978
Rabbit anti-N-cadherin	Proteintech; 22018-1-AP
Rabbit anti-FGFBP1	Proteintech; 25006-1-AP
Rabbit anti-EGR1	Cell Signal Technology; 4154s
Rabbit anti-Ki67	Servicebio; GB111141
Rabbit anti-PCNA	Servicebio; GB11010
Rabbit anti-p-FGFR1(phospho Y654)	Abcam; ab59194
Rabbit anti-FGF2	Beyotime; AF6891
Rabbit anti-Cleaved-PARP	Cell Signal Technology;94885S
anti-mouse IgG, HRP-linked Antibody	Cell Signal Technology; 2624S
anti-rabbit IgG, HRP-linked Antibody	Cell Signal Technology; 3670S
anti-goat IgG, HRP-linked Antibody	Servicebio; GB23204
anti-sheep IgG, HRP-linked Antibody	Abcam; ab6900
iF488-Tyramide	Servicebio; G1231
iF555-Tyramide	Servicebio; G1233
iF647-Tyramide	Servicebio; G1232
Alexa Fluor® 488 Goat anti-Rabbit	Invitrogen; A-11035

Supplemental Table 8. List of primer sequences for the RT-qPCR assay.

Gene	Forward primer	Reverse primer
<i>CDH1</i>	TCTCTCACGCTGTGTCATCC	CACTGGATTTGTGGTGACGA
<i>CDH2</i>	AGGCGTCTGTAGAGGCTTCTGG	TCTGCTGACTCCTTCACTGACTCC
<i>VIM</i>	GTCCGTGTCCTCGTCCCTCCTAC	AGTTGGCGAAGCGGTCATTTCAG
<i>FAP</i>	TACCCAAAGGCTGGAGCTAA	ACAGGACCGAAACATTCTGG
<i>FGFBP1</i>	TCTGGGCAACACCCAGAT	GGCATGAGGTTGGATTGC
<i>SNAIL</i>	CCTGGTCAAGAAGCATTTCACGC	GGAGGAGGTGTCAGATGGAGGAG
<i>FGF1</i>	ACAGCCCTGACCGAGAAGTT	CCGTTGCTACAGTAGAGGAGT
<i>FGF2</i>	AGAAGAGCGACCCTCACATCA	CGGTTAGCACACACTCCTTTG
<i>FGF7</i>	TCCTGCCAACTTTGCTCTACA	CAGGGCTGGAACAGTTCACAT
<i>FGF10</i>	CAGTAGAAATCGGAGTTGTTGCC	TGAGCCATAGAGTTTCCCCTTC
<i>FGF21</i>	GCCTTGAAGCCGGGAGTTATT	GTGGAGCGATCCATACAGGG
<i>FGFR1</i>	GGCTACAAGGTCCGTTATGCC	GATGCTGCCGTACTCATTCTC
<i>FGFR2</i>	GGTGGCTGAAAAACGGGAAG	AGATGGGACCACACTTTCATA

<i>FGFR3</i>	CCCAAATGGGAGCTGTCTCG	CCCGGTCCTTGTCATGCC
<i>FGFR4</i>	GAGGGGCCGCCTAGAGATT	CAGGACGATCATGGAGCCT
<i>IL1B</i>	CCACAGACCTTCCAGGAGAATG	GTGCAGTTCAGTGATCGTACAGG
<i>IL33</i>	GCCTGTCAACAGCAGTCTACTG	TGTGCTTAGAGAAGCAAGATACTC
<i>CSF2</i>	GGAGCATGTGAATGCCATCCAG	CTGGAGGTCAAACATTTCTGAGAT
<i>IL-18</i>	GATAGCCAGCCTAGAGGTATGG	CCTTGATGTTATCAGGAGGATTCA
<i>CXCL5</i>	CAGACCACGCAAGGAGTTCATC	TTCTTCCCCTTCTTCAGGGAG
<i>EGR1</i>	AGCAGCACCTTCAACCCTCAGG	GAGTGGTTTGGCTGGGGTAACT
<i>ACTB</i>	TCTTCCAGCCTTCCCTTCTG	CCTGCTTGCTGATCCACATC
<i>C4B</i>	AGATGCGGTGTCCAAGGTTCTG	GTTGCCAGGTATTTCCAAGGTCC
<i>HSP90AB4P</i>	GGAAGACCACTTGGCAGTCAAG	CAAAGCCGACATACTCTGGCATC
<i>SERPIN1</i>	AGCTCAGCATGGTCATCCTGCT	CGAGATTCTCAGGTTTAGTCCAC
<i>IGFBP6</i>	CACAGGATGTGAACCGCAGAGA	CACTGAGTCCAGATGTCTACGG
<i>PLCH1</i>	CTTTGGTTCGGTTCCTTGTGTGG	CTTTGGTTCGGTTCCTTGTGTGG
<i>GAL</i>	TCAGGTATGGACCTGTCAAAGCT	TGGCAACCACAGGTCATTACAGC
<i>TMSB10</i>	TGGCAGACAAACCAGACATGG	CGAAGAGGACGGGGGTAGG

Supplemental Table 9. List of antibodies for the Western blotting and ChIP assays.

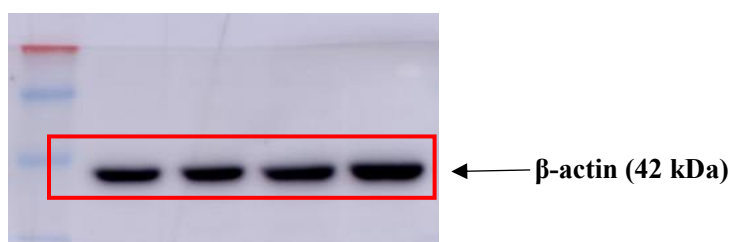
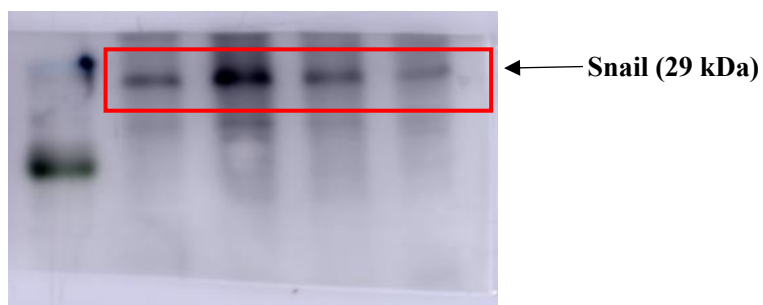
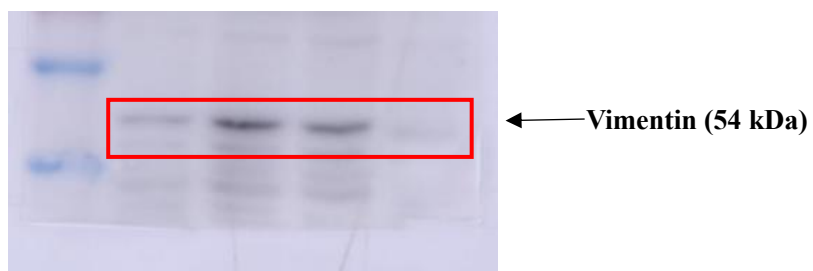
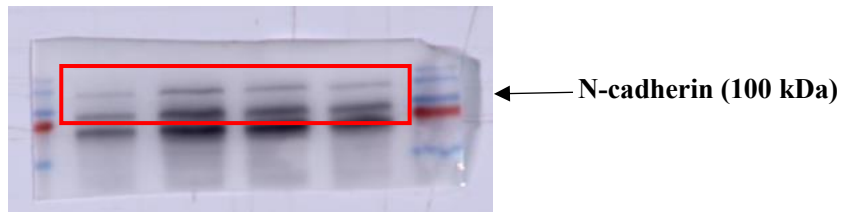
Antibodies	Supplier; catalogue number
Sheep anti-FAP α	R&D System; AF3715
Mouse anti- β -actin	Cell Signal Technology; 3700S
Mouse anti-E-Cadherin	Cell Signal Technology; 14472S
Rabbit anti-N-Cadherin	Cell Signal Technology; 4061S
Mouse anti-Vimentin	Abcam; ab8978
Rabbit anti-Snail	Abcam; ab180714
Rabbit anti-FGFBP1	Proteintech;25006-1-AP
Rabbit anti-FGFR1	Cell Signal Technology; 9740s
Rabbit anti-p-FGFR1(phospho Y654)	Abcam; ab59194
Rabbit anti-FGF2	Beyotime; AF6891
Rabbit anti-EGR1	Cell Signal Technology; 4154s
Rabbit anti-Erk1/2	Cell Signal Technology; 4695s
Rabbit anti-p-Erk1/2 (Thr202/Tyr204)	Cell Signal Technology; 4370s
Rabbit anti-HIF1 α	Cell Signal Technology; 36169s

anti-mouse IgG, HRP-linked Antibody	Cell Signal Technology; 2624s
anti-rabbit IgG, HRP-linked Antibody	Cell Signal Technology; 5127s
anti-sheep IgG, HRP-linked Antibody	Abcam; ab6900
anti-Rabbit IgG	Cell Signal Technology; 2729s

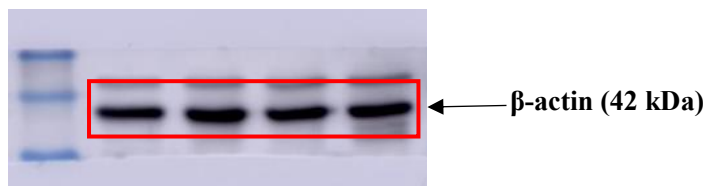
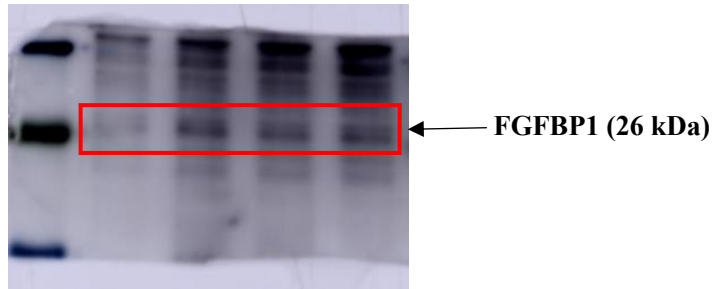
Supplemental Table 10. List of primer sequences for the ChIP-qPCR assay.

Gene promoter	Forward primer	Reverse primer
<i>FAP</i>	AGCACACCTTGGATATTACTC	ATGAGTCATTAGGCACTTAC
<i>FGFBP1</i>	GCCAGGAACTCTACCATAGGT	TTGGTGGTAAGGTTTCACAGGT

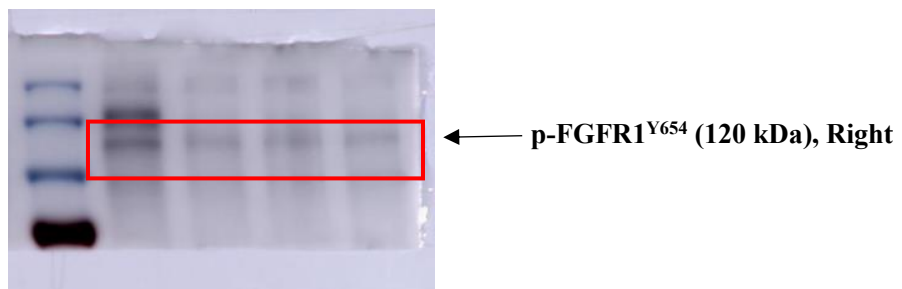
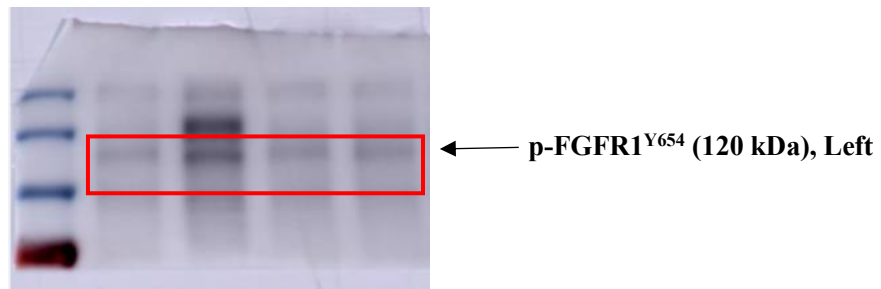
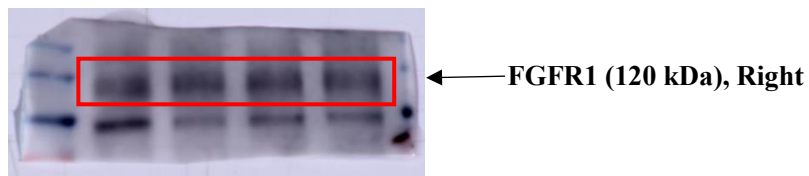
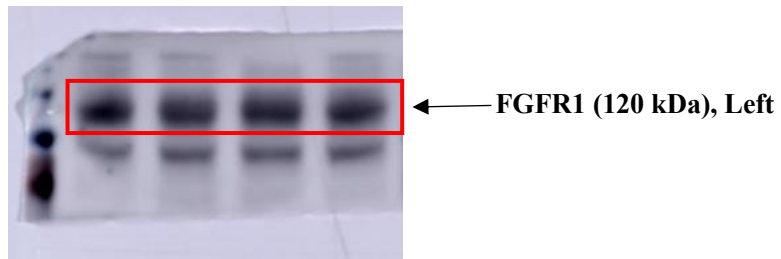
Full unedited gel for Figure 3I



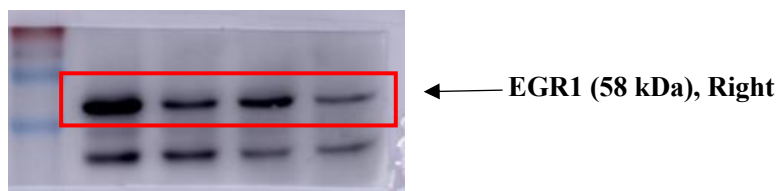
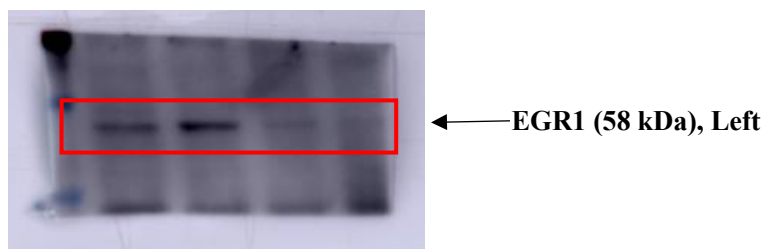
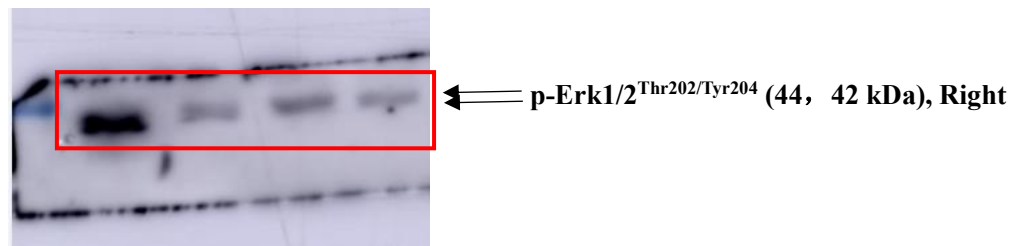
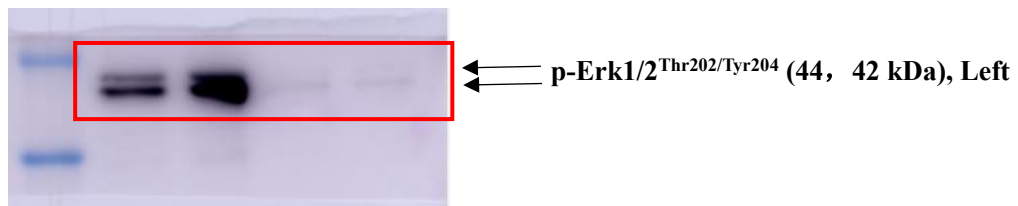
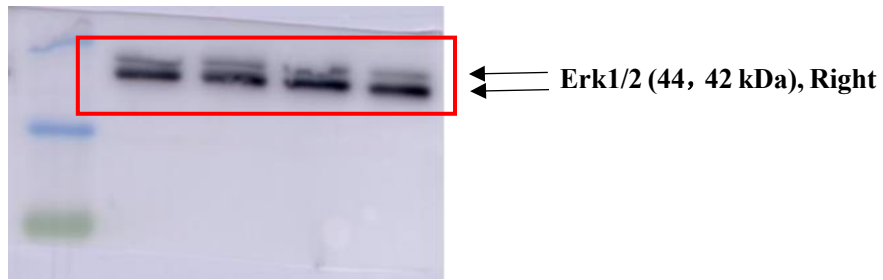
Full unedited gel for Figure 4C



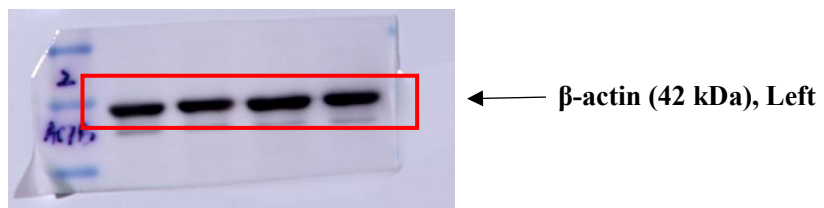
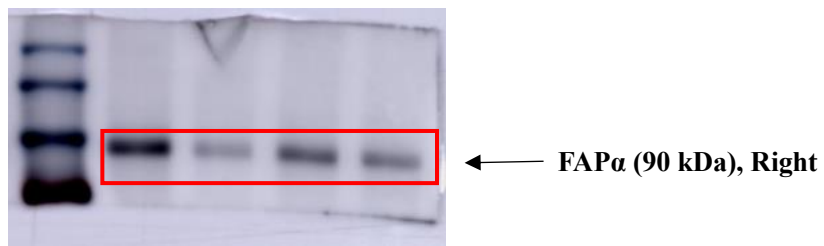
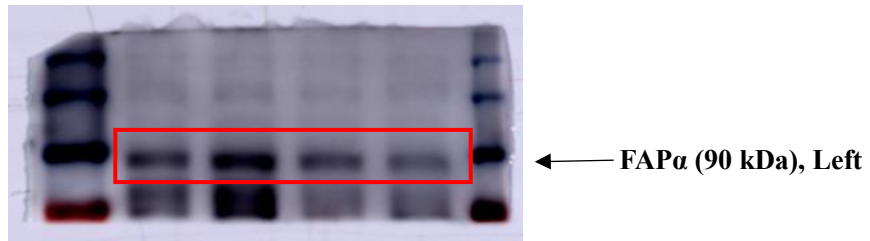
Full unedited gel for Figure 5A



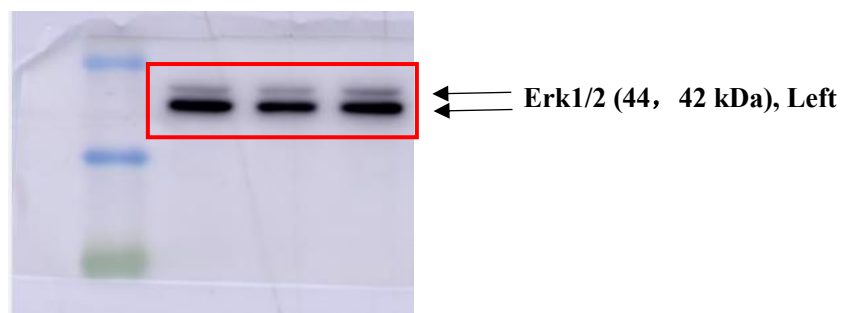
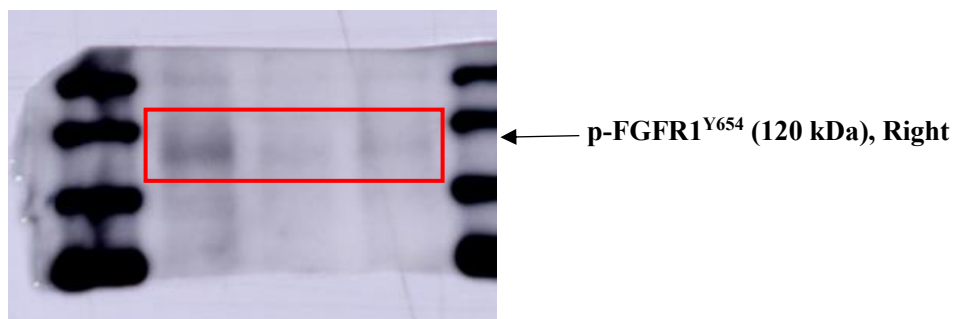
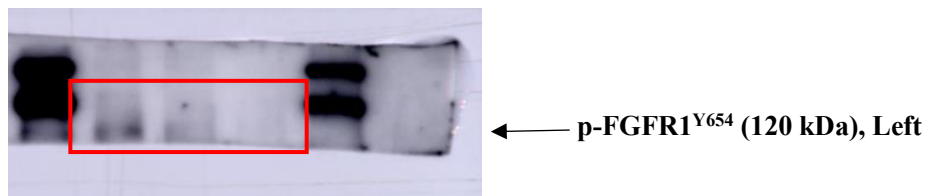
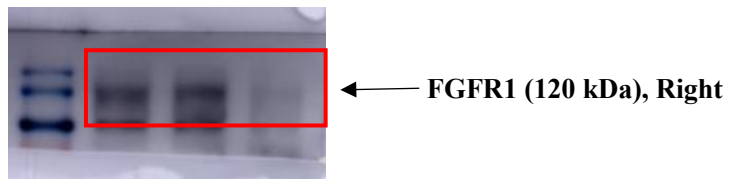
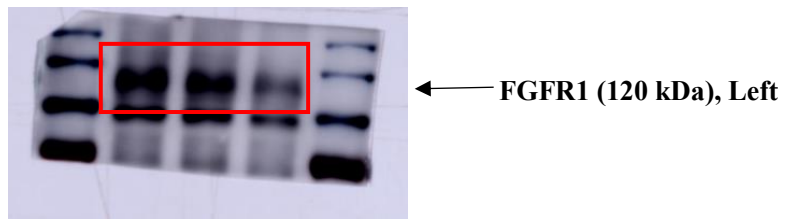
Full unedited gel for Figure 5A



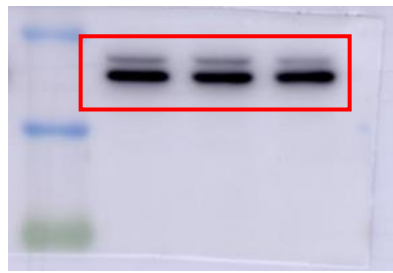
Full unedited gel for Figure 5A



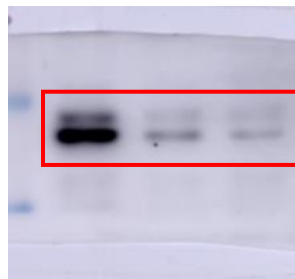
Full unedited gel for Figure 5B



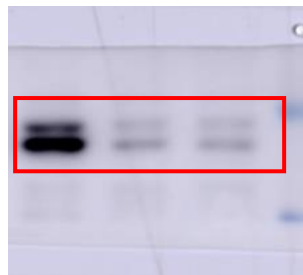
Full unedited gel for Figure 5B



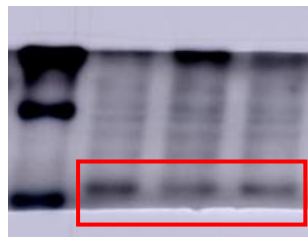
←← Erk1/2 (44, 42 kDa), Right



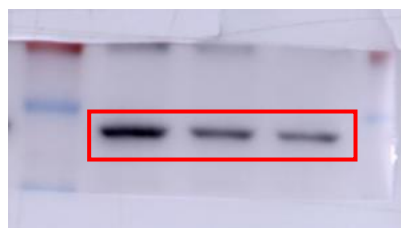
←← p-Erk1/2^{Thr202/Tyr204} (44, 42 kDa), Left



←← p-Erk1/2^{Thr202/Tyr204} (44, 42 kDa), Right

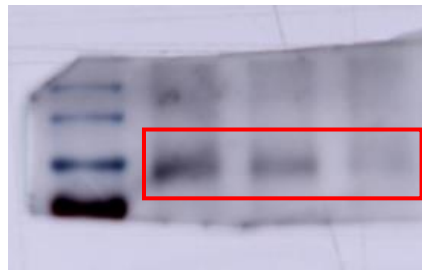


← EGR1 (58 kDa), Left

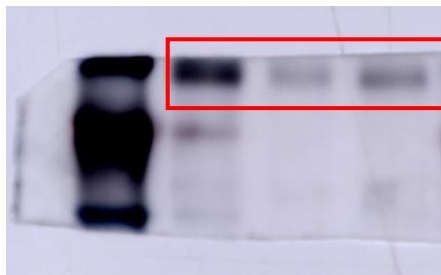


← EGR1 (58 kDa), Right

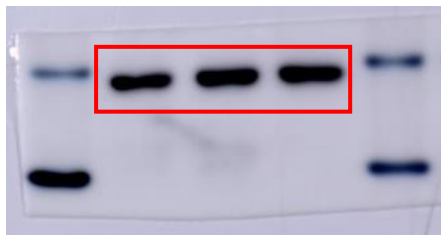
Full unedited gel for Figure 5B



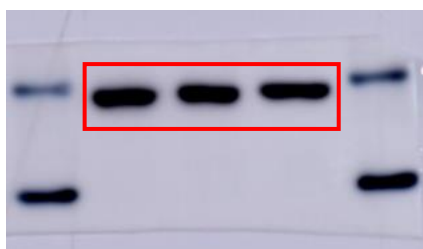
← FAPα (90 kDa), Left



← FAPα (90 kDa), Right

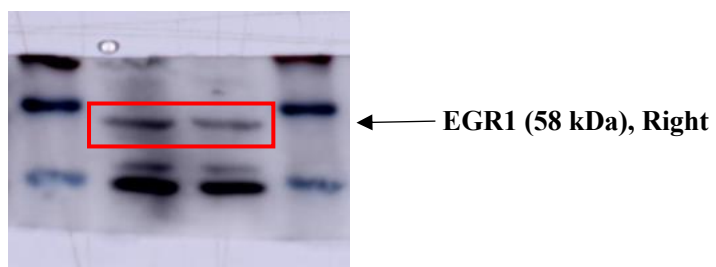
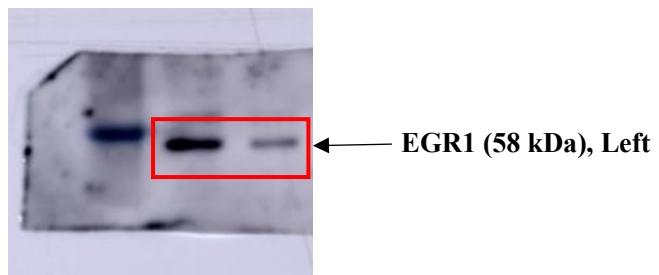
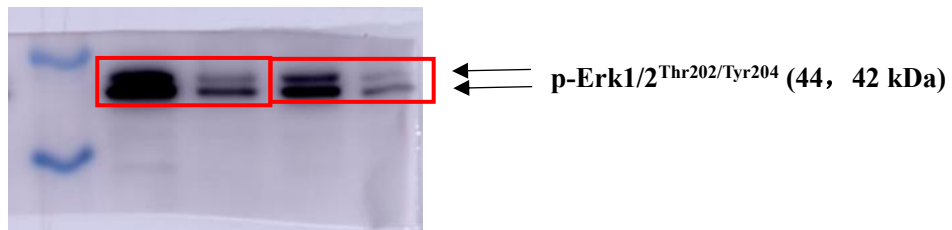
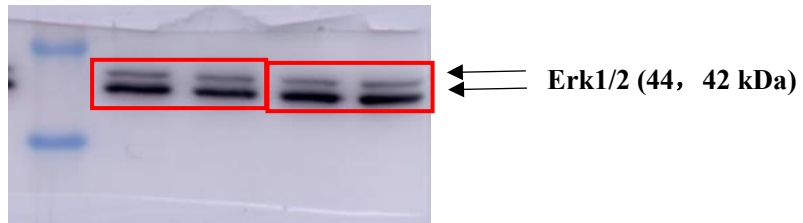


← β-actin (42 kDa), Left

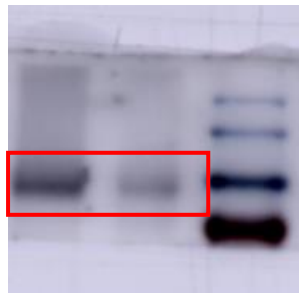


← β-actin (42 kDa), Right

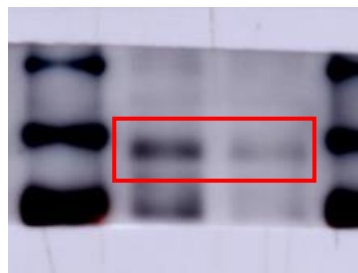
Full unedited gel for Figure 5C



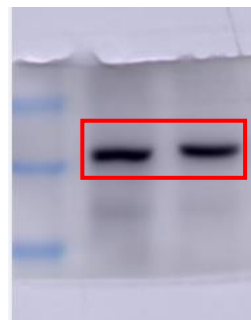
Full unedited gel for Figure 5C



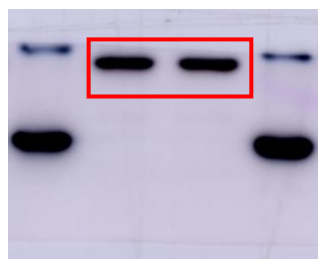
← FAP α (90 kDa), Left



← FAP α (90 kDa), Right



← β -actin (42 kDa), Left

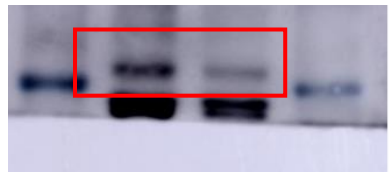


← β -actin (42 kDa), Right

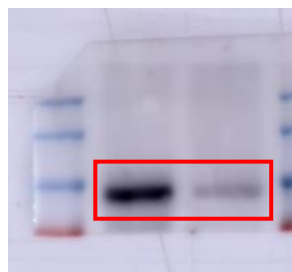
Full unedited gel for Figure 5D



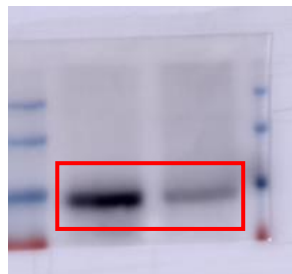
← EGR1 (58 kDa), Left



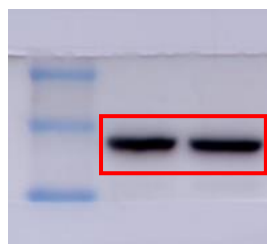
← EGR1 (58 kDa), Right



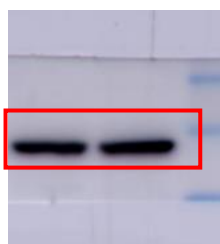
← FAPα (90 kDa), Left



← FAPα (90 kDa), Right

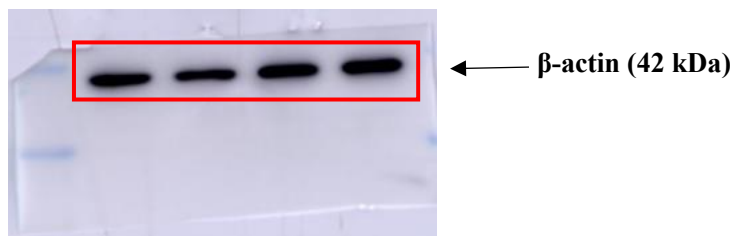
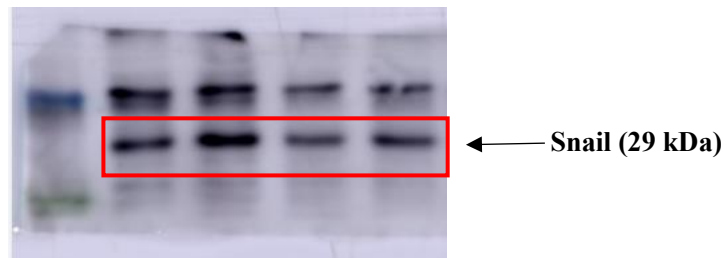
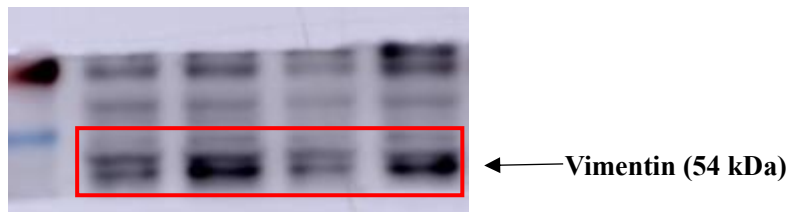
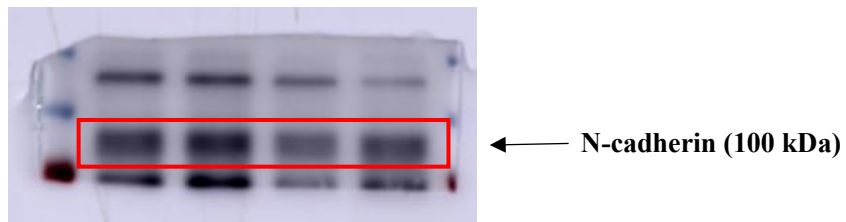
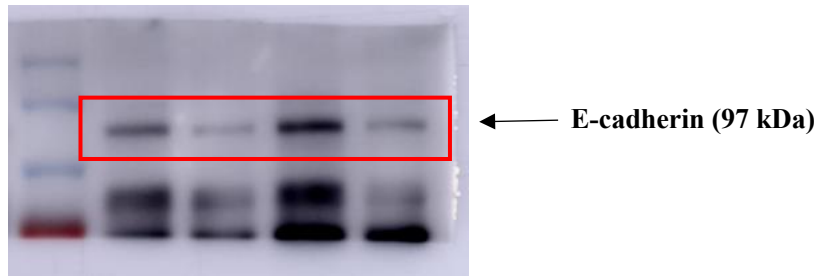


← β-actin (42 kDa), Left

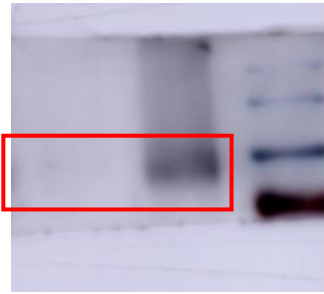


← β-actin (42 kDa), Right

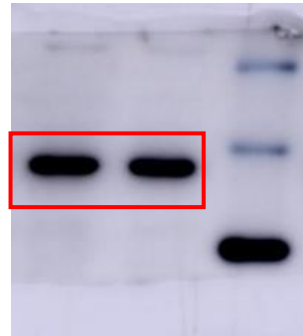
Full unedited gel for Figure 6J



Full unedited gel for Supplemental Figure 3B

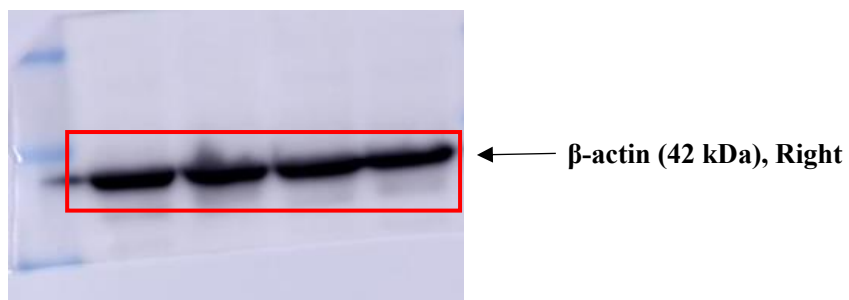
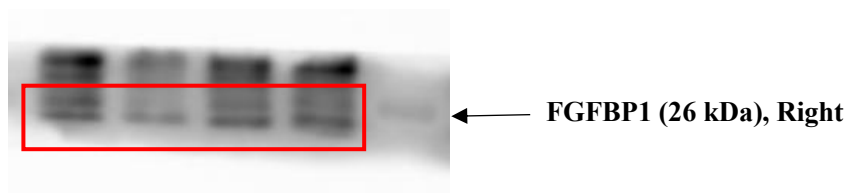
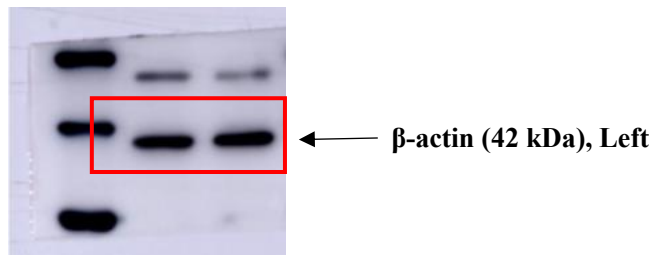
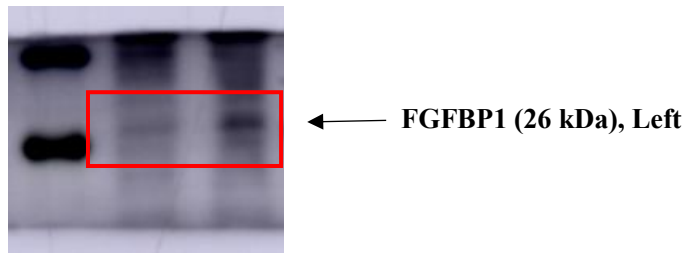


← **FAPα (90 kDa)**

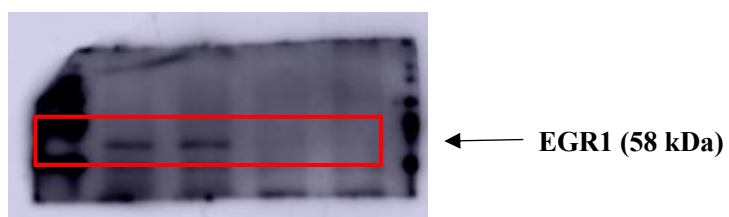
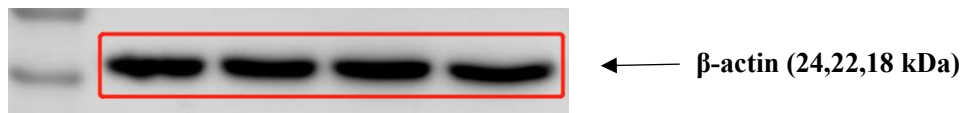
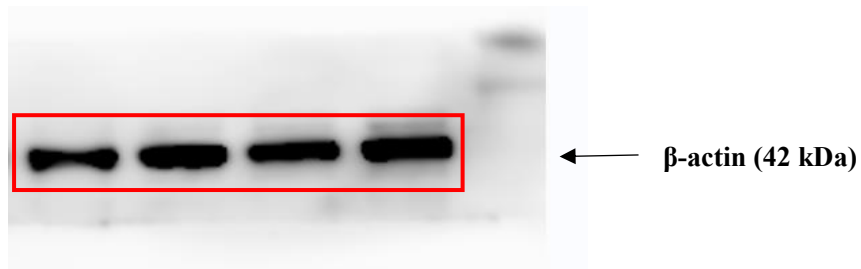
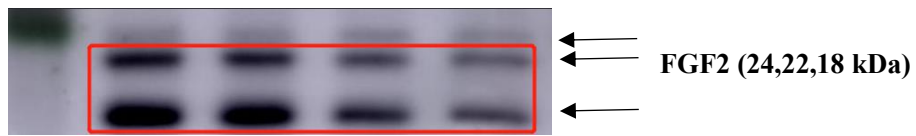


← **β-actin (42 kDa)**

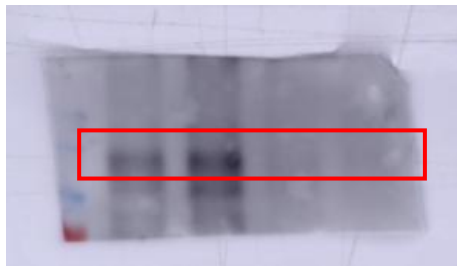
Full unedited gel for Supplemental Figure 4E



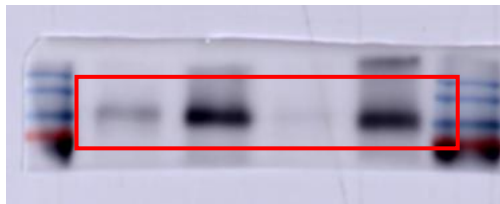
Full unedited gel for Supplemental Figure 7A



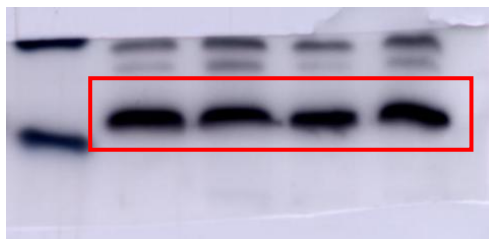
Full unedited gel for Supplemental Figure 11A



← FGFR1 (120 kDa)



← FAP α (90 kDa)

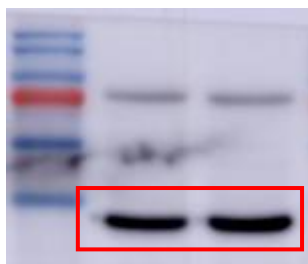


← β -actin (42 kDa)

Full unedited gel for Supplemental Figure 14C

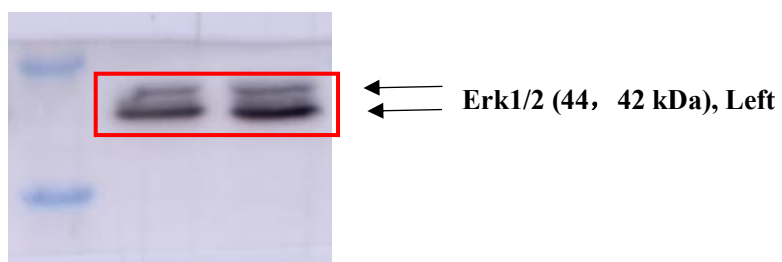
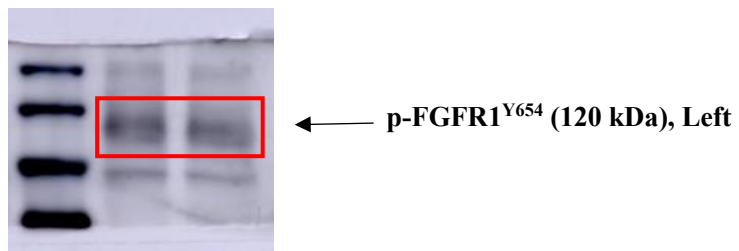
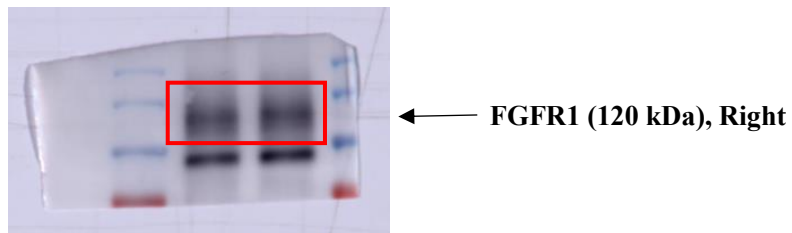
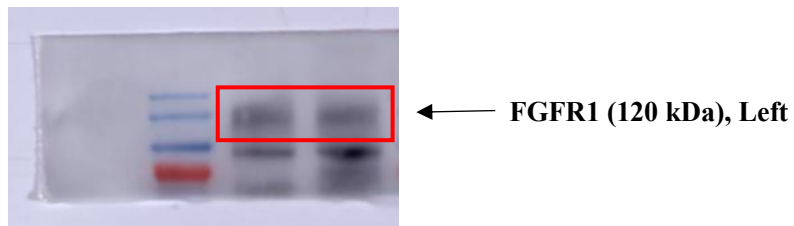


← FGFBP1 (26 kDa)

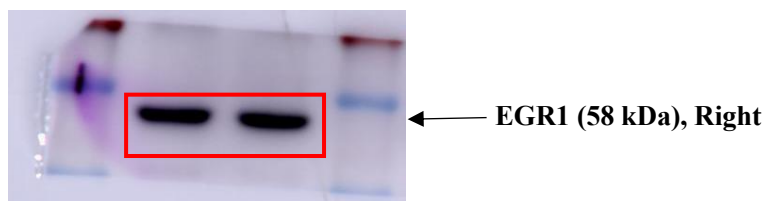
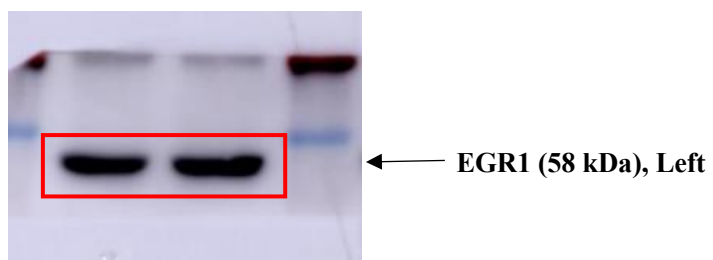
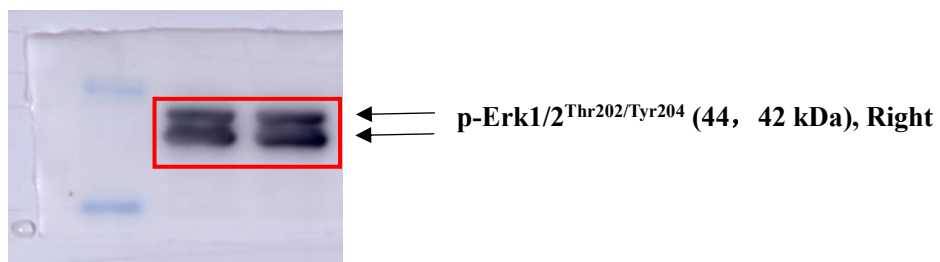
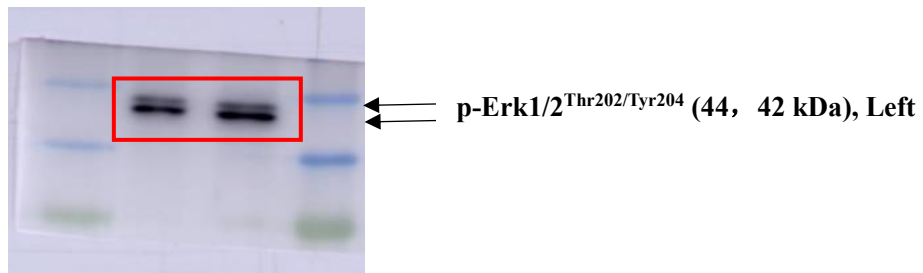
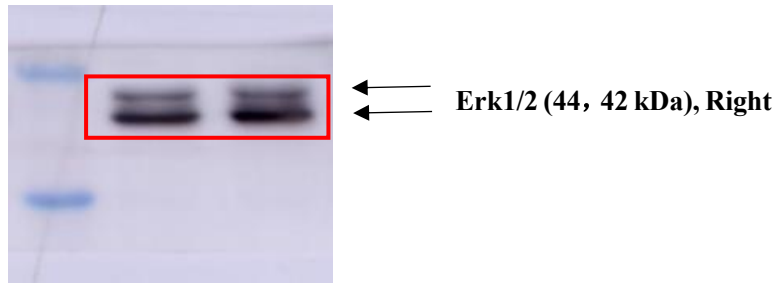


← β -actin (45 kDa)

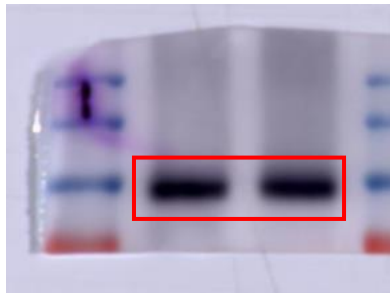
Full unedited gel for Supplemental Figure 14D



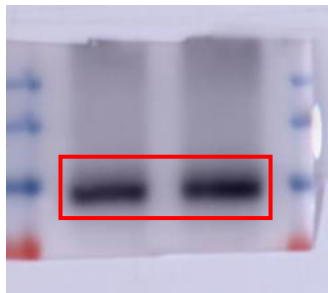
Full unedited gel for Supplemental Figure 14D



Full unedited gel for Supplemental Figure 14D



← **FAP α (90 kDa), Left**



← **FAP α (90 kDa), Right**



← **β -actin (42 kDa), Left**

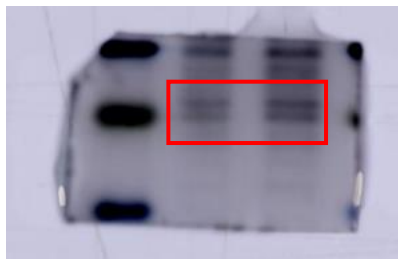


← **β -actin (42 kDa), Right**

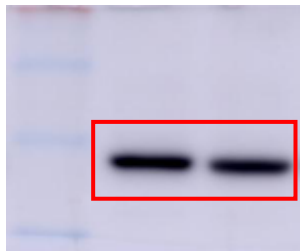
Full unedited gel for Supplemental Figure 15B



← HIF-1 α (120 kDa)



← FGFBP1 (26 kDa)



← β -actin (42 kDa)

Full unedited gel for Supplemental Figure 15C

