SUPPORTING INFORMATION (SI) APPENDIX

Supplementary Materials and Methods

Cell culture. OE19 and OE33 cells (ATCC, Manassas, VA) were maintained in RPMI containing 8% fetal bovine serum (FBS), L-glutamine (2mM), penicillin (100 units/mL), and streptomycin (500 μg/mL) (Lonza, Basel, Switzerland) and cultured according to standard procedures. Carboplatin, paclitaxel, 5-fluorouracil, cisplatin, and eribulin were obtained from the pharmacy of the Academic UMC. Recombinant IL-6 was used at 2 ng/ml (R&D), CCL2 was used at 5ng/ml (R&D), and HGF was used at 5ng/ml (Sino Biological Inc). TGF-β was used at 5 ng/mL. Neutralizing antibodies against IL-6 (R&D), CCL2 (R&D), HGF (Sino Biological Inc.) were used at a concentration of 500 ng/ml unless indicated otherwise.

Cell viability assay. Cell viability was determined using the Cell Titer-Blue Cell Viability Assay kit (Promega). Tumor cells were seeded into 96-well plates at a density of 1000-2000 cells/well in triplicates. After cell adhesion overnight, baseline cell viability was measured and treatment was started (see below). Cell viability was determined by adding 20µl Cell Titer-Blue reagent to each well, 3-hour incubation at 37°C, and plate read-out was performed on a cytofluormeter (BioTek Instruments, Winooski, VT). Cell viability was calculated by comparing the values obtained from the unconditioned and/or untreated control cells versus the conditioned and/or treated cells. The values were controlled for baseline cell viability. The following therapeutic agents were administered once at the indicated concentrations and incubated for the indicated time; 5-fluorouracil (5-FU), carboplatin, cisplatin, eribulin, and paclitaxel. The indicated supernatants, recombinant proteins, and neutralizing antibodies were refreshed every three days during the assays, in the concentrations as stated above. The supernatants were obtained from 081RF (80% confluency) and 243RF (30% confluency) cultures, which were incubated for three and five days, respectively. The control cells received 1:4 diluted unconditioned fibroblast medium. To exclude effects on drug response due to the use of different culture media, cell viability assays were performed on 007B and 031M cultured in DMEM/F12 or DMEM/F12 – IMDM 1:1 and showed no difference in response to carboplatin or paclitaxel (*SI Appendix,* Fig. S1 *E* and *F*).

Immunofluorescence. Immunofluorescence was performed as previously described (1). Images were acquired using a confocal microscope (Confocal SP8-X SMD, Leica, Amsterdam, the Netherlands). Phase contrast images were obtained using a Zeiss microscope (Axiovert 200M). The used antibodies were diluted in wash buffer (PBS with 0.1% Triton X-100 and 1% normal goat serum) and are listed in Supplementary Table 1.

Quantitative RT-PCR. RNA was isolated (Macherey Nagel), and cDNA was synthesized using Superscript III (Invitrogen). Quantitative Reverse Transcription-PCR (qRT-PCR) was performed using SYBR green (Roche) on a Lightcycler LC480II (Roche), according to manufacturer's protocols. Values were normalized to *GAPDH* according to the comparative threshold cycle (Cp) method. Primer sequences are summarized in Supplementary Table 2.

Flow cytometry. Flow cytometric stainings were performed as previously described (2). Data were analyzed with FlowJo 10 (Tree Star, Ashland, OR). Intracellular epitopes were measured using permeabilization buffer (BD Biosciences), in these conditions no PI was used. The values represent the geometric mean fluorescence (gMFI) intensity of the appropriate channel corrected for the isotype control, yielding the delta gMFI. The used antibodies and isotype controls are listed in Supplementary Table 1.

IL-6 measurements on cell cultures. Human IL-6 ELISA DuoSet (R&D systems) was performed on three days conditioned supernatant from OE19, OE33, 007B, 031M, 081RF, 117BF and 268BF cells (all at 80% confluency) and five days conditioned supernatant from 243RF cells (30% confluent). The appropriate unconditioned medium was used as control. Measurements were performed in triplicates and calculated according to a standard curve, according to the manufacturer's protocol. Levels of IL-6 found in CAF supernatants did not exceed the detection range of the ELISA. For mouse CAFs, mouse IL-6 ELISA DuoSet was used. Range for IL-6 ELISA was 1-4000pg/ml; range for ADAM12 ELISA was 0-18659pg/ml.

Migration assay. Prior to the assay, cells were cultured for 2 weeks in either control medium or medium supplemented with 2 ng/ml IL-6, 25% 081RF supernatant or 25% 081RF supernatant that was pre-incubated with IL-6 neutralizing antibody for 30 minutes. Cells were passed or medium was refreshed every three days. The migration was measured every 2 minutes for 3h at

37°C using a cytofluorometer (BioTek Instruments) and was controlled for the no-attractant control.

Survival, gene set enrichment analysis and gene correlations. Data were obtained from TCGA (The Cancer Genome Atlas) study (Study ID: TCGA-ESCA)(3), and selected to contain EAC only. Samples were dichotomized by median *IL6*, *CCL2* or *HGF* expression and survival analysis was performed according to the Log-rank (Mantel-Cox) test. Data were plotted using GraphPad Prism 7. Gene set enrichment analysis (GSEA (4)) as performed using the Broad Institute software (http://www.broadinstitute.org/gsea/index.jsp). Samples were dichotomized by median expression. 1000 permutations were run on the phenotype. To identify the most significant differentially expressed genes in respect to the stromal infiltration gene set, the R2: Genomics Analysis and Visualization Platform was used (http://r2.amc.nl).

Limiting dilution assay. Prior to the assay, cells were cultured for two weeks in control medium or medium supplemented with 2 ng/ml IL-6, 25% 081RF supernatant or 25% 081RF supernatant that was pre-incubated with IL-6 neutralizing antibody. Cells were sorted into 96 wells, per plate accordingly; 16x1, 16x2, 16x4, 8x8, 8x16, 8x32, 8x64, 8x128, and 8x254 cells/well on a BD FACSAria III. Clonogenic potential was determined using the Extreme Limiting Dilution Analysis (ELDA) software: http://bioinf.wehi.edu.au/software/elda/. Data are represented as percent clonogenic potential. The culture conditions were maintained for 6 weeks and refreshed once a week.

In vivo assays

To allow IL-6 transsignaling in a xenograft model, we established primary EAC cells that overexpress human IL-6 ligand (for autocrine signaling), or the mouse IL-6 receptor (for paracrine signaling). FLAG-tagged ORFs for *hIL6* (OHu23477D) and *mIL6Ra* (OMu18873) in *pcDNA3.1* were obtained from GenScript. (Leiden, Netherlands). To allow efficient gene transfer to our primary tumor lines, EcoRI restriction sites were added to both the 5' and 3' ends of the ORF by PCR, and these were used to clone into pTOPO to verify ORF sequence. EcoRI sites were then used to transfer the inserts into the *pLEGO-iV2* lentiviral vector (5). Third generation lentivirus production was used and 031M cells were transduced and subsequently FACS-sorted for Venus/GFP. IL-6 levels were confirmed by ELISA as for Figure 2. Expression of mIL-6R was verified by immunofluorescence as for Figure S1, using M2 anti-FLAG (see Supplementary

Table 1). Next, cells were injected in immunodeficient mice (Envigo, Horst, Netherlands) at $5x10^5$ cells in 50% Matrigel/medium. 6 mice were grafted per group, and monitored for a period of 100 days. Tumors were measured using calipers. Ethical approval was obtained (LEX269AA), and mice were housed and handled at the local animal facility according in full accordance with local and European legislation.

Supplementary Figures S1 to S11 and Tables S1 and S2

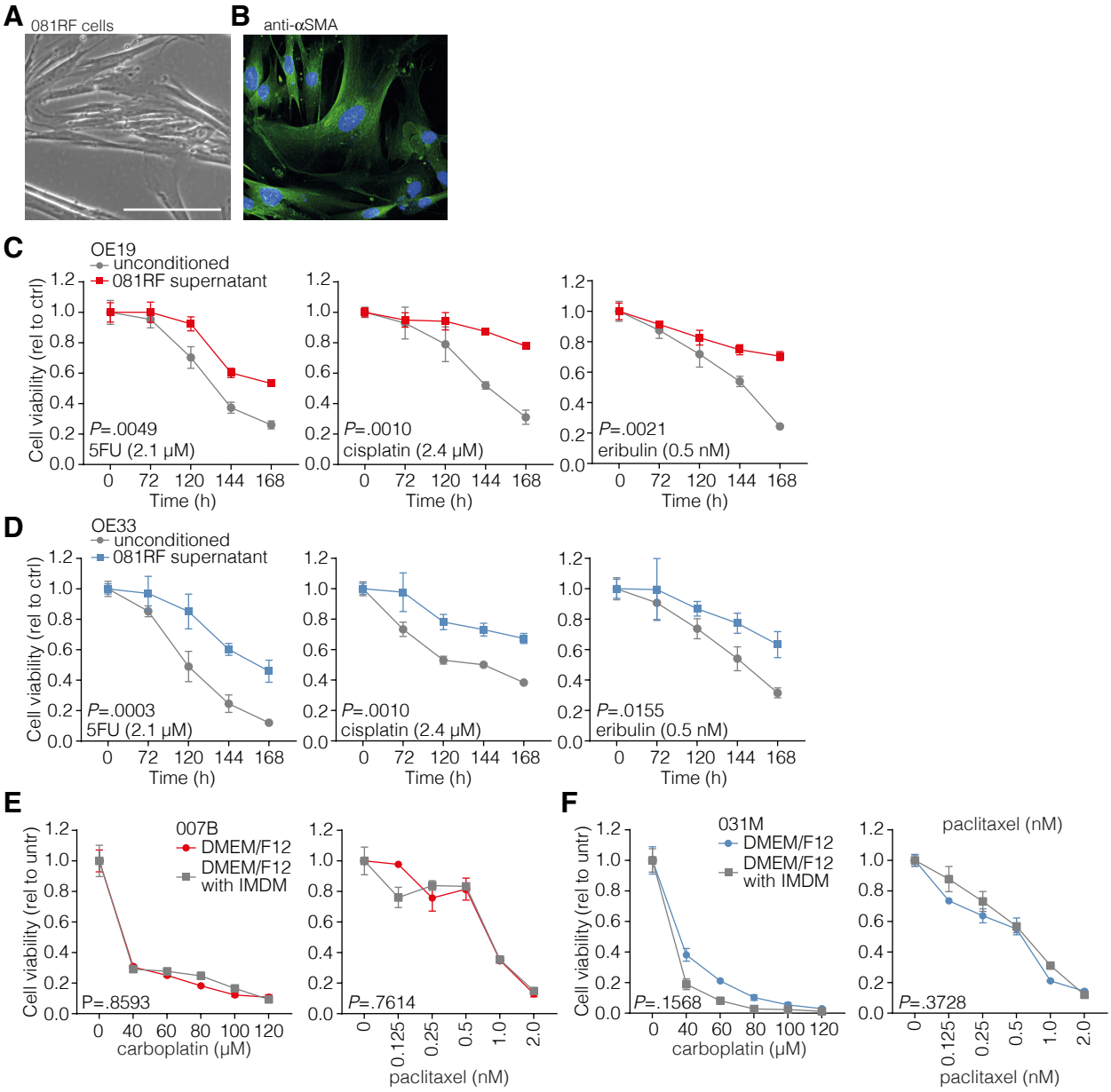


Fig. S1 CAF supernatant confers chemoresistance. (*A*) 081RF cells were isolated from a resected tumor and after an adherent culture was established, morphology was assessed by phase-contrast microscopy. Scale bar: 200μm. (*B*) 081RF cells were processed for immunofluorescence against α-SMA. Magnification as for panel *A*. (*C*) Cell viability assays were performed on OE19 cells exposed to the indicated chemotherapeutics and concentrations with

unconditioned control medium (grey lines) or medium supplemented with 081RF supernatant (1 in 4 diluted, colored lines). Graphs show means ± SEM of data normalized to t=0, n = 3. *P*-values were determined by two-way ANOVA and Bonferroni correction. (*D*) As for *C*, using the OE33 cell line. (*E)* CAF culture medium was tested for effect on treatment response; Cell viability assays were performed on 007B primary cells exposed to the indicated chemotherapeutics and concentrations cultured in DMEM/F12 medium (colored lines) or DMEM/F12 mixed with IMDM medium 1:1 (grey lines). (*F*) As for *E*, using 031M cells.

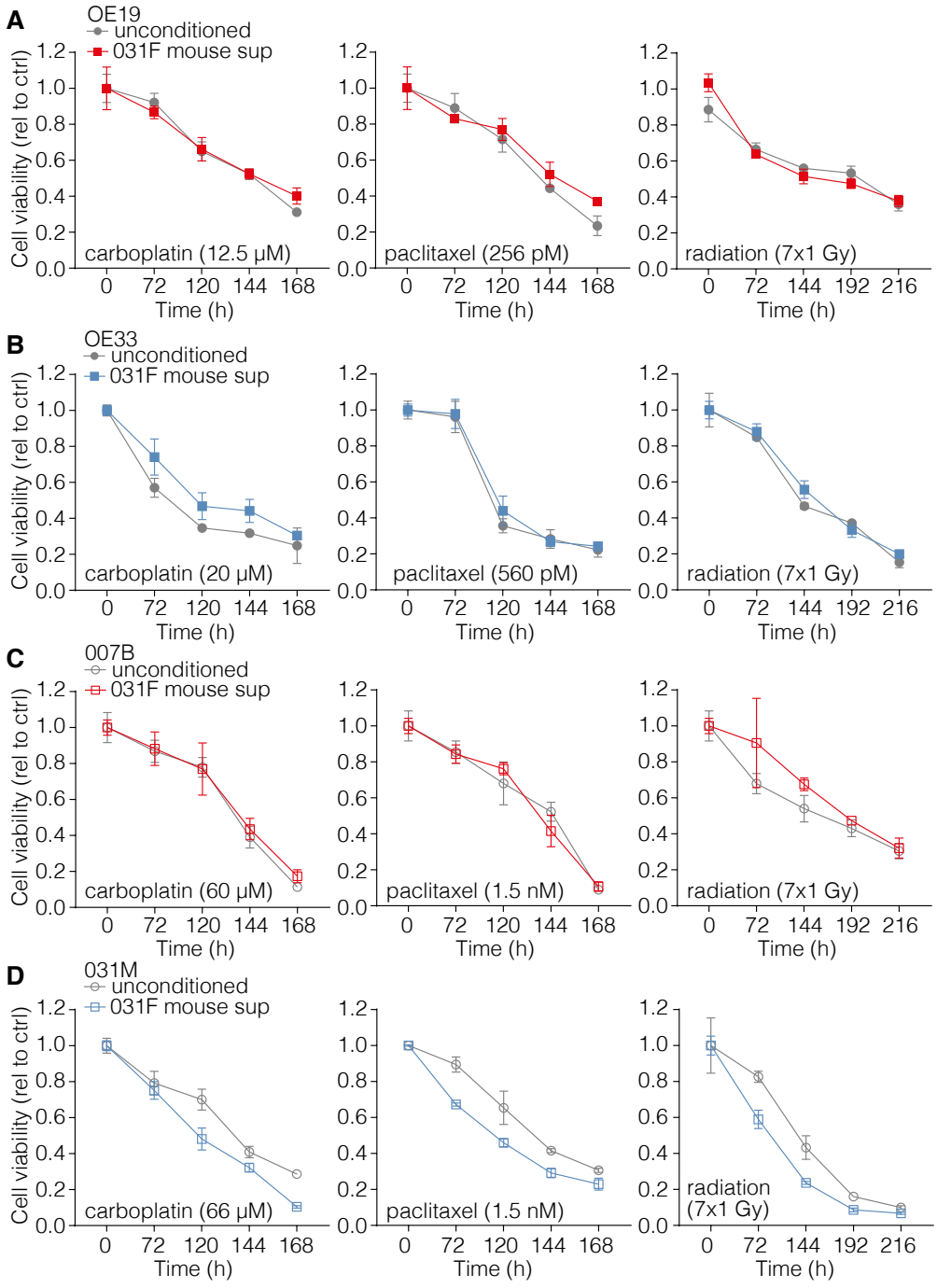


Fig. S2 Mouse CAF supernatant does not confer chemoresistance to human EAC cells. (*A*) OE19 cells were incubated with the indicated chemotherapeutics and concentrations or radiated 7 times with 1Gy, cultured in control medium (grey lines) or medium supplemented with supernatant from mouse CAFs (031F, 1 in 4 diluted, colored lines), and cell viability was measured. Graphs show means ± SEM of data normalized to t=0, n = 3. (*B-D*) As for *A*, using OE33, 007B, and 031M cells.

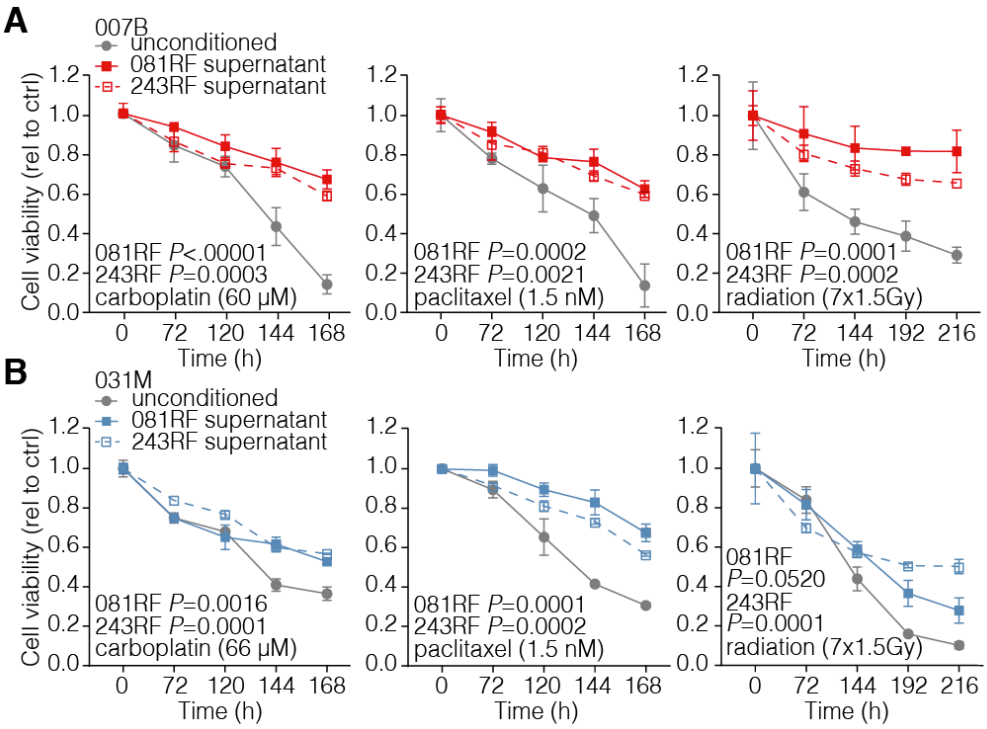


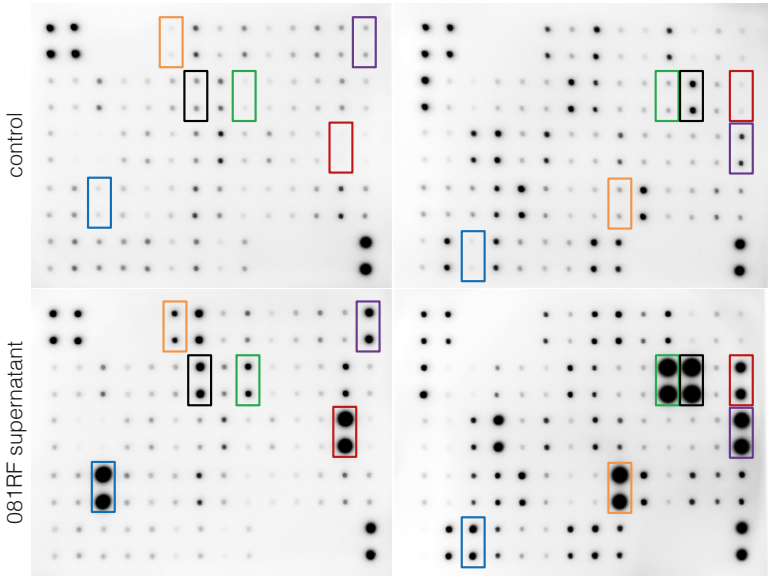
Fig. S3. Therapy resistance is driven by CAF-secreted cytokines. (*A*) Cell viability assays were performed on primary 007B cells exposed to the indicated chemotherapeutics and concentrations, with control unconditioned medium (grey lines), medium supplemented with 081RF supernatant (colored lines), or medium supplemented with 243RF supernatant (also 1 in 4 diluted; open symbols and dashed lines). Graphs show means ± SEM of data normalized to t=0, n = 3. *P*-values were determined by two-way ANOVA and Bonferroni correction. (*B*) As for a, using primary 031M cells.

A

human cytokine array

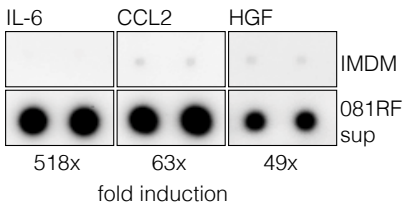
membrane 1

membrane 2



Cytokine	Fold induction	Cytokine	Fold induction
IL-6	518	HGF	49
CCL2	63	TIMP-2	36
GM-CSF	28	GRO	27
Angiogenin	17	TNFRSF11B	22
CCL11	11	CXCL8	8
CXCL6	7	CXCL1	5

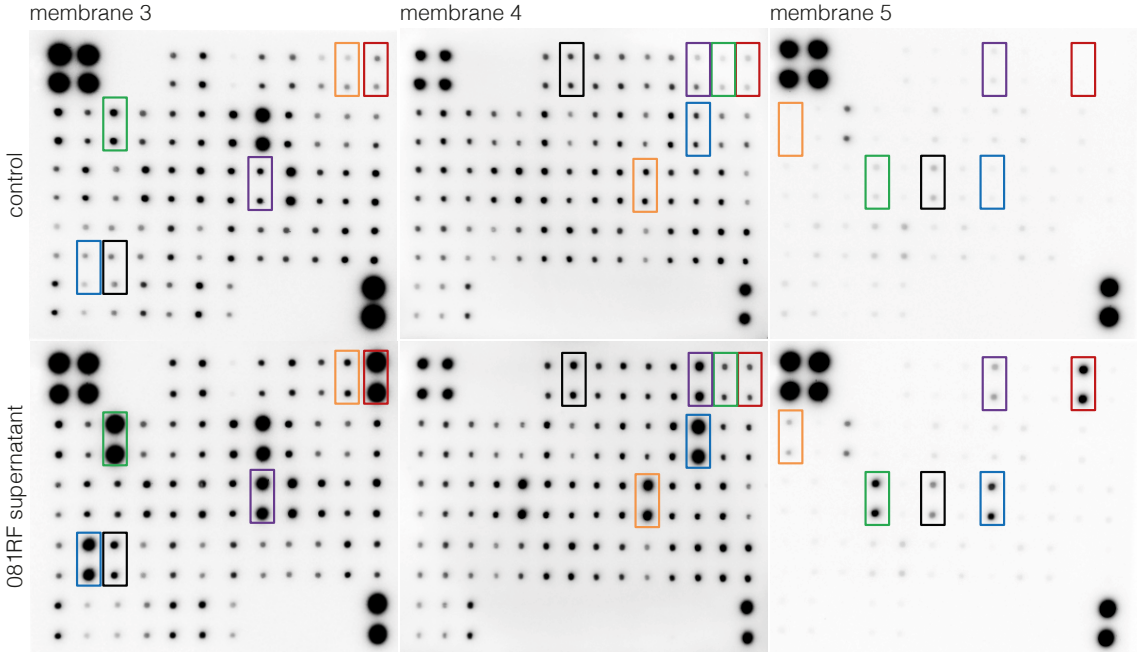
B



membrane 3

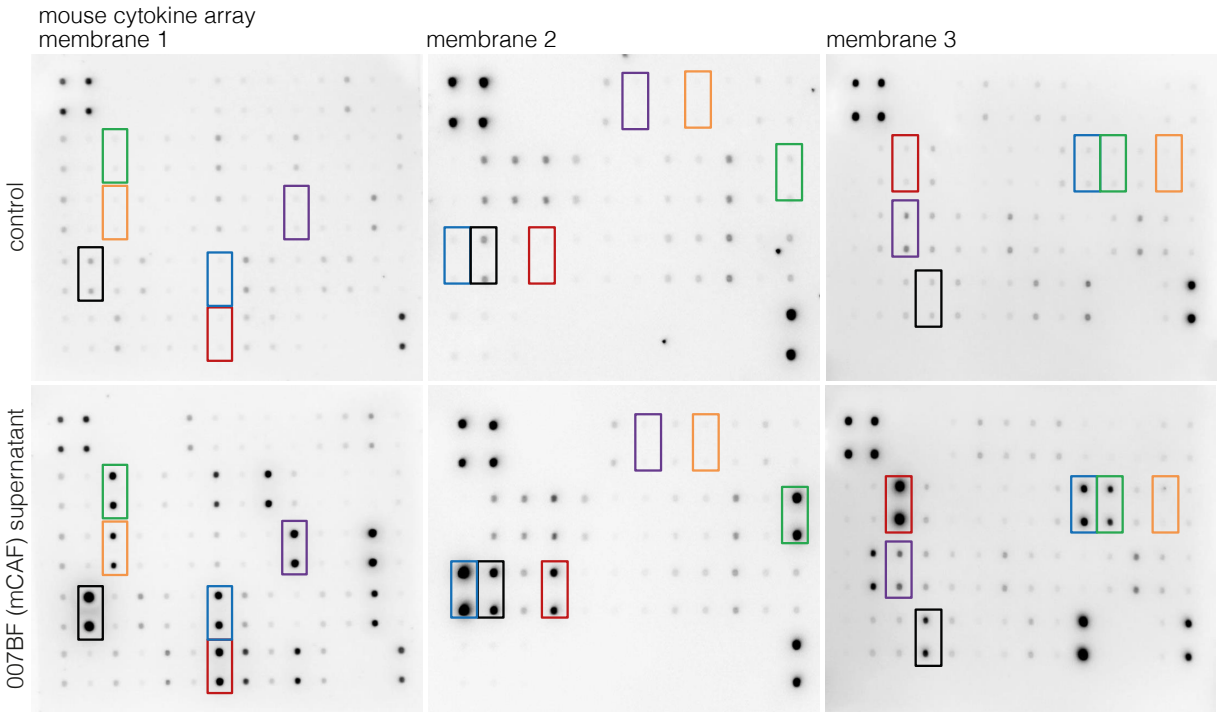
membrane 4

membrane 5



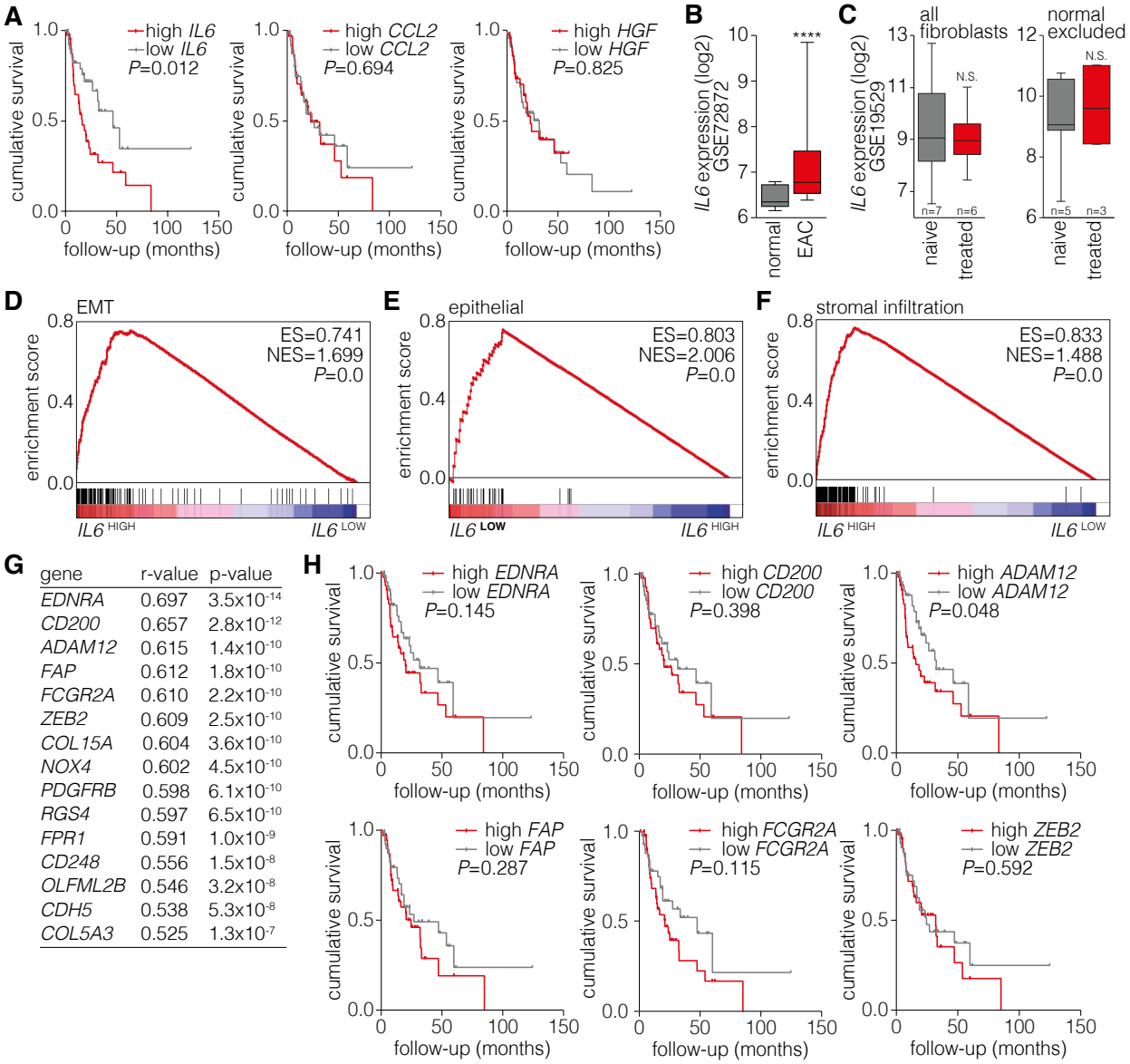
Cytokine	Fold induction	Cytokine	Fold induction	Cytokine	Fold induction
Follistatin	16	CD14	6	Beta-2M	44
PAI-1	10	MMP-3	6	CD26	26
GDF-15	4	CXCL16	4	Decoin	14
FLRG	4	MMP-1	3	Beta IG-H3	6
MMP-10	4	DR6	3	ANGPT1	5
CXCL4	3	ALCAM	2	DKK-3	2

Fig. S4 Cytokine array reveals human CAF-secreted cytokines. (*A*) An AAH-CYT-4000 (RayBiotech, Norcross, GA) cytokine array of 5 membranes was used to analyze supernatant incubated on 081RF cells for 3d, unconditioned medium was used as control. Color-coded text corresponds to matching boxes on membrane scans. Fold induction was determined by measuring spot intensity in Image J, and calculated after correction for the negative and positive controls on the membranes and dividing by the unconditioned control. (B) Crop, magnification, and fold inductions are shown of the three highest induced cytokines from membranes shown in panel *A.*



Cytokine	Fold induction	Cytokine	Fold induction	Cytokine	Fold induction
TNF R1	96	Pro-MMP-9	143	Decorin	57
MIP-1γ	80	MMP-3	107	Galectin-1	30
Fractalkine	51	MMP-2	30	Gas1	28
IL-6	51	E-selectin	9	GITR ligand	20
CXCL1	46	CD26	9	HGF	10
CCL2/MCP-1	41	Osteoprotegerin	7	Pentraxin-3	9

Fig. S5 Cytokine array reveals mouse CAF-secreted cytokines. An Mouse Cytokine Array C2000 (RayBiotech, Norcross, GA) cytokine array of 3 membranes was used to analyze supernatant incubated on mouse CAFs as for Figure S4. Top 5 induced cytokines per membrane are shown.



gene	r-value	p-value
EDNRA	0.697	$3.5x10^{-14}$
CD200	0.657	$2.8x10^{-12}$
ADAM12	0.615	$1.4x10^{-10}$
FAP	0.612	$1.8x10^{-10}$
FCGR2A	0.610	$2.2x10^{-10}$
ZEB2	0.609	$2.5x10^{-10}$
COL15A	0.604	$3.6x10^{-10}$
NOX4	0.602	$4.5x10^{-10}$
PDGFRB	0.598	$6.1x10^{-10}$
RGS4	0.597	$6.5x10^{-10}$
FPR1	0.591	$1.0x10^{-9}$
CD248	0.556	$1.5x10^{-8}$
OLFML2B	0.546	$3.2x10^{-8}$
CDH5	0.538	$5.3x10^{-8}$
COL5A3	0.525	$1.3x10^{-7}$

Fig. S6 High *IL6* expression correlates with poor outcome and EMT in EAC. (*A*) EAC samples from the TCGA set, were dichotomized by median *IL6, CCL2, HGF* and survival analysis was performed using Kaplan-Meier analysis and Log-rank statistical test. (*B*) *IL6* expression levels derived from EAC and esophageal healthy tissue using the Krause *et al.* dataset (6). Statistical significance was tested using the Mann-Whitney test. *P*<.0001. (*C*) *IL6* expression in fibroblasts from treatment naive and treated tissue was queried in the Saadi *et al.* dataset (GSE19529; (7)). (*D*) Gene set enrichment analysis (GSEA;) on EAC samples from the TCGA set, dichotomized by median *IL6* expression demonstrates a correlation between *IL6* high samples and an EMT signature. ES, enrichment score; NES, normalized enrichment score. The EMT signature was adapted and pooled from refs (8, 9) (n=122 genes). (*E*) As for panel *D*, demonstrating a

correlation between *IL6* low samples and an epithelial gene signature (note that the phenotype order is from low to high), which consisted of the following genes; *CDH1, MAL2, MAP7, RAB25, CLDN4, ELF3, SPINT2, MARVELD2, CD24, AP1M2, MAPK13, DSP, ERBB3, GALNT3, AP1M2, CLDN7, ST14, KRT19, TMPRSS4, GPX2, TOX3, PRSS8, PKP3, SPINT1, MARVELD3, CEACAM5, CGN, MYH14, FXYD3, CEACAM6*. (*F*) As for panel *D*, using a stromal infiltration gene set (10), demonstrating a correlation between *IL6*-high samples and the used stromal infiltration gene set. (*G*) *IL6* gene expression was correlated with indicated stromal infiltration-related genes using the EAC TGCA set and the significantly associated individual genes are shown. (*H*) TCGA set EAC samples were dichotomized by median for the top 6 genes from panel *G*, and survival analysis was performed using Kaplan-Meier analysis and Log-rank statistical test. *ADAM12*, third graph in the top row, was the only gene to significantly associate with survival.

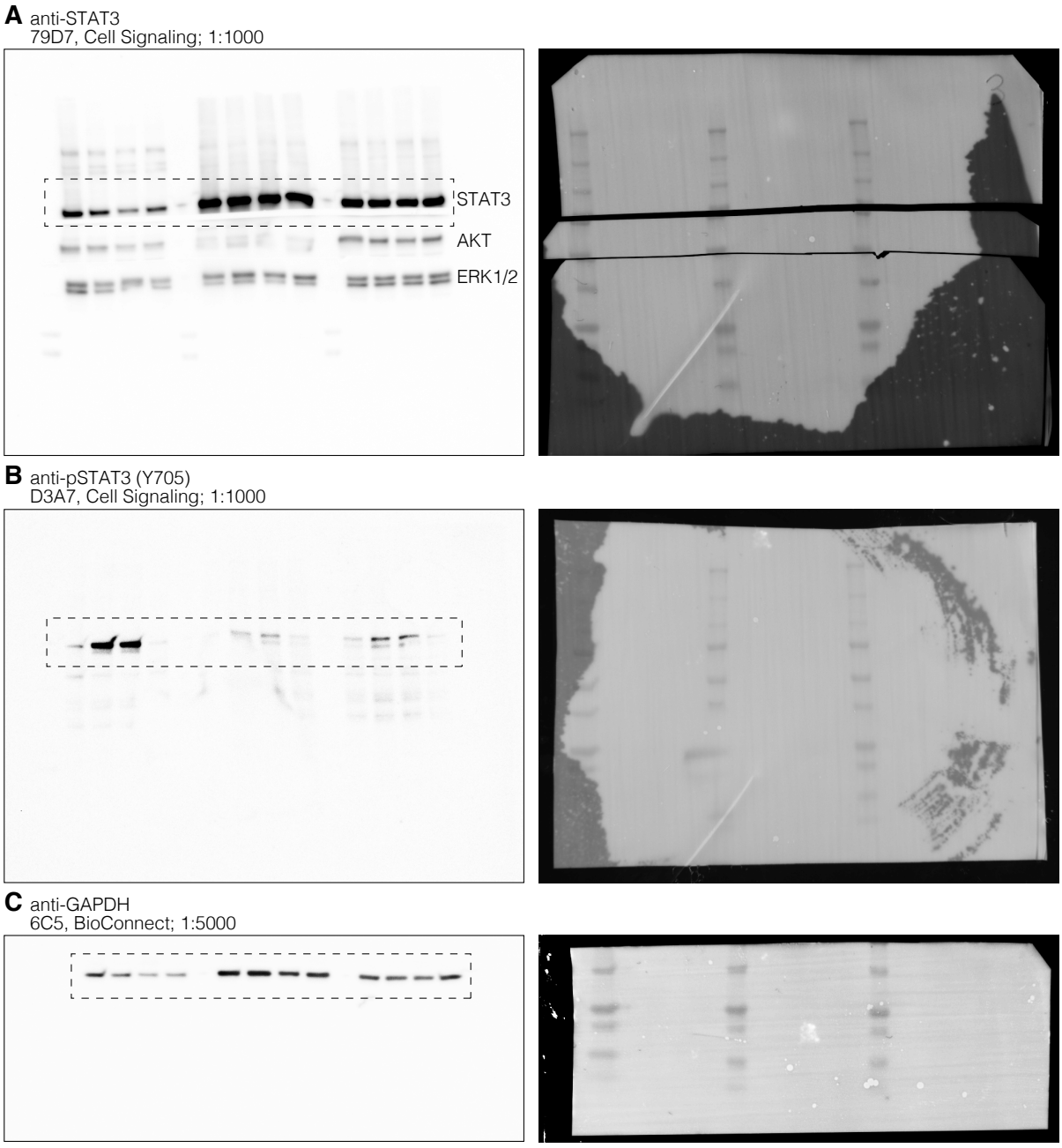


Fig. S7 Membrane processing for Western blot. (*A-C*) Lysates were run on 3 separate SDS-PAGE gels and transferred to PVDF membranes. Following transfer, membranes were cut guided by the molecular weight markers, as shown in right hand panels. Following incubation with antibodies against indicated proteins, ECL was performed yielding the images in the left hand panels. Dashed boxes indicate the crops that are shown in Fig. 2*I*.

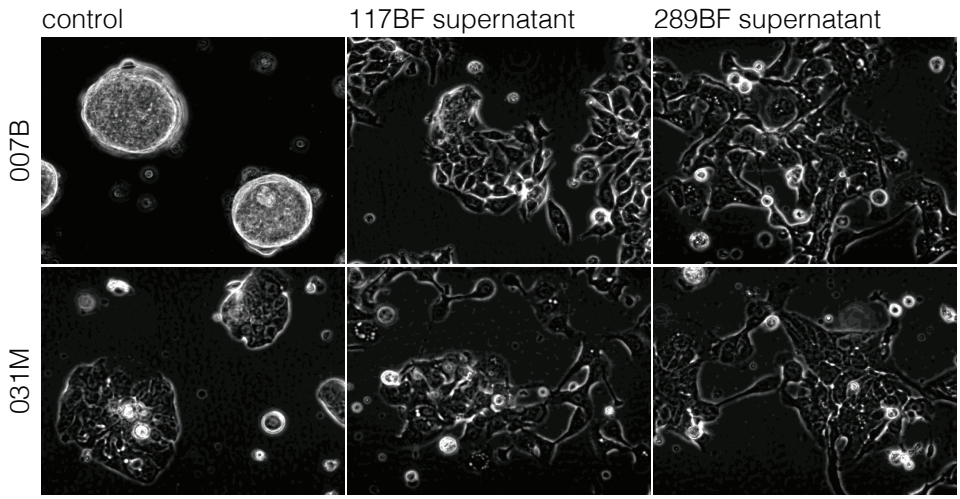


Fig. S8 Treatment naive CAF supernatant induces epithelial-to-mesenchymal transition. 007B and 031M cells were treated as for Figure 3, using supernatant from treatment-naive 117BF and 289BF CAFs.

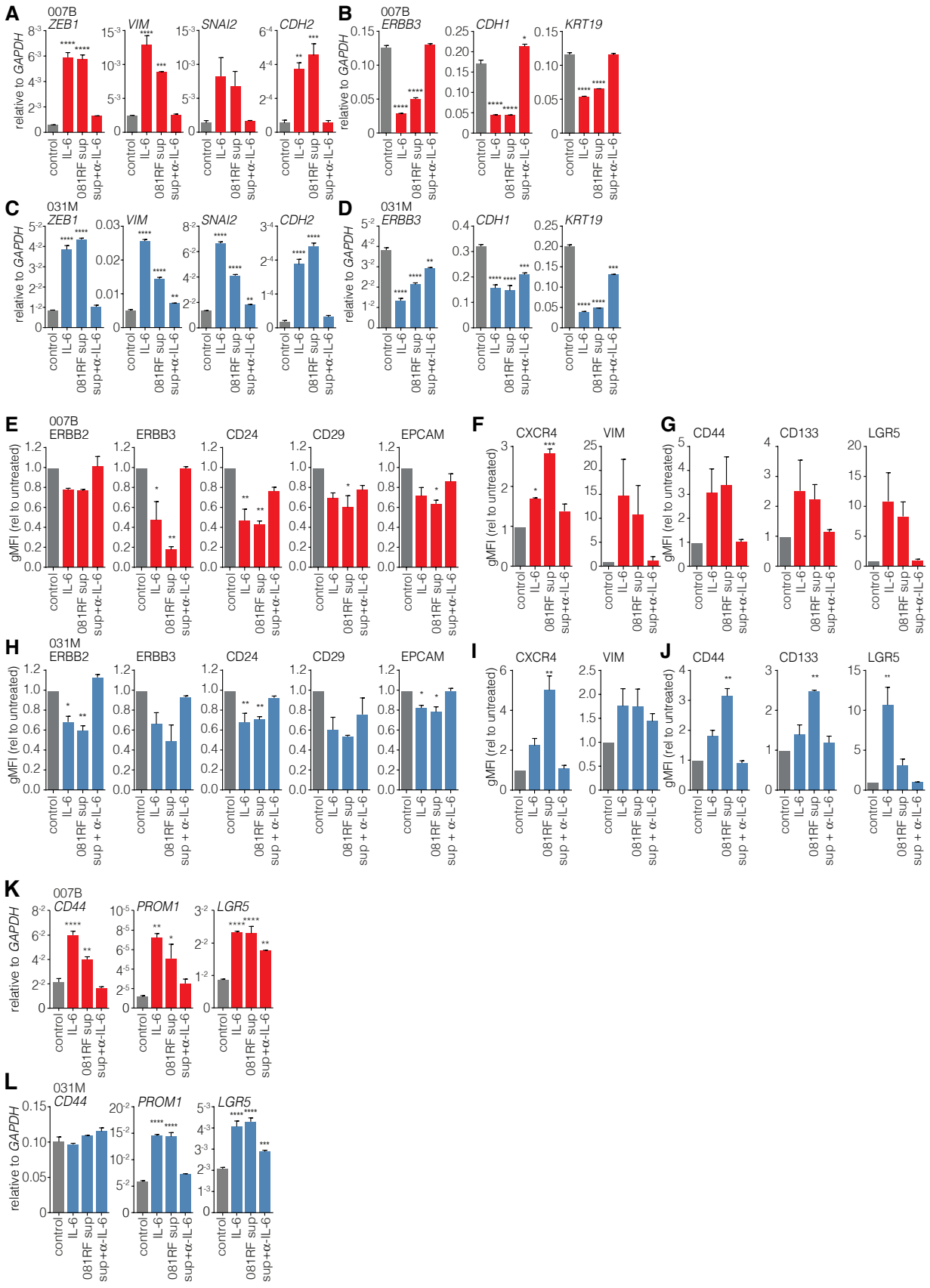

A
007B
ZEB1
VIM
SNAI2
CDH2
relative to GAPDH
B
007B
ERBB3
CDH1
KRT19
C
031M
D
E
ERBB2
CD24
CD29
EPCAM
gMFI (rel to untreated)
F
CXCR4
VIM
G
CD44
CD133
LGR5
H
I
J
K
PROM1
L
control
IL-6
081RF sup
sup+α-IL-6
sup + α-IL-6

Fig. S9 Molecular characterization of IL-6 dependent cell state shifts. (*A*) Transcript analysis for mesenchymal genes in 007B cells cultured as for Figure 3: Cells were cultured for 14 days in the following conditions; control, recombinant IL-6, 081RF supernatant (1 in 4 diluted), 081RF supernatant + IL-6 neutralizing antibody. Data were normalized to the control condition, bar graphs show means ± SEM, n = 3. **P* < .05, ***P* < .01, ****P* < .001, and *****P*<.0001. (*B*) As for panel *A*, for epithelial genes. Significance was tested by two-sided unpaired *t* tests compared to the control. (*C* and *D*) As for panel *A* and *B*, using 031M cells. (*E-G*) Staining by flow cytometry for indicated epithelial, mesenchymal, and stem cell markers in 007B cells. (*H-J*) As for panel *A–D*, using 031M cells. (*K-L*) Transcript analysis of cancer stem cell markers in 007B and 031M cells.

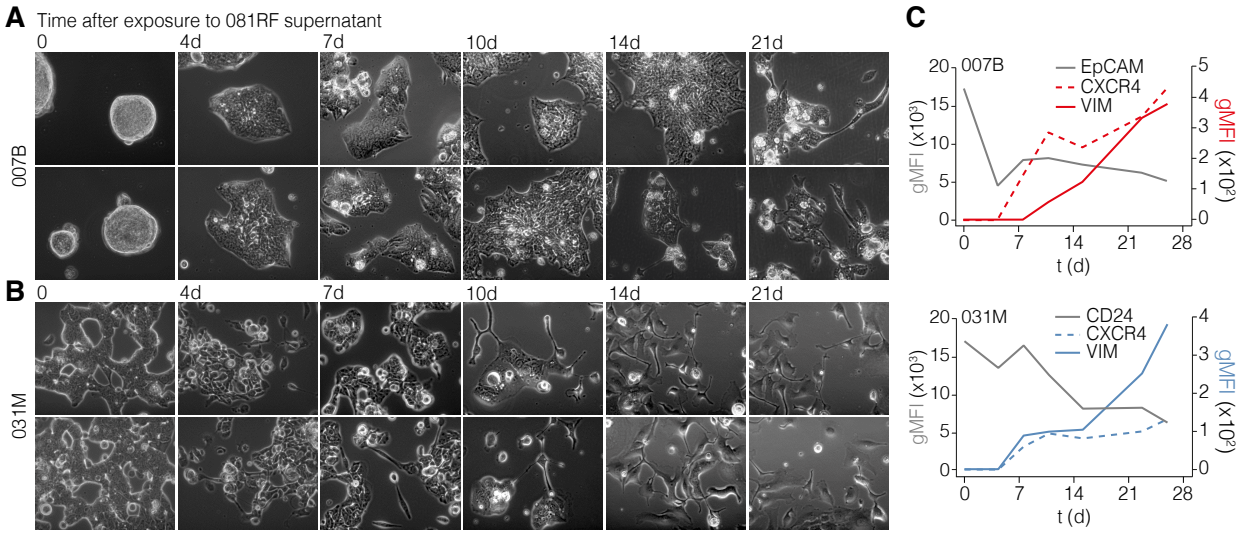


Fig. S10 Kinetics of EMT in response to CAF supernatant. (*A*) 007B primary EAC cells were exposed to 081RF CAF supernatant as for Figure 3*A*. At the indicated time points, cells were imaged by brightfield microscopy. (*B*) As for panel A, using 031M cells. (*C*) Cells shown in panels A-B were harvested and expression of epithelial cell surface markers (grey lines, left y-axis) and mesenchymal markers (colored lines, right y-axis) were determined by FACS.

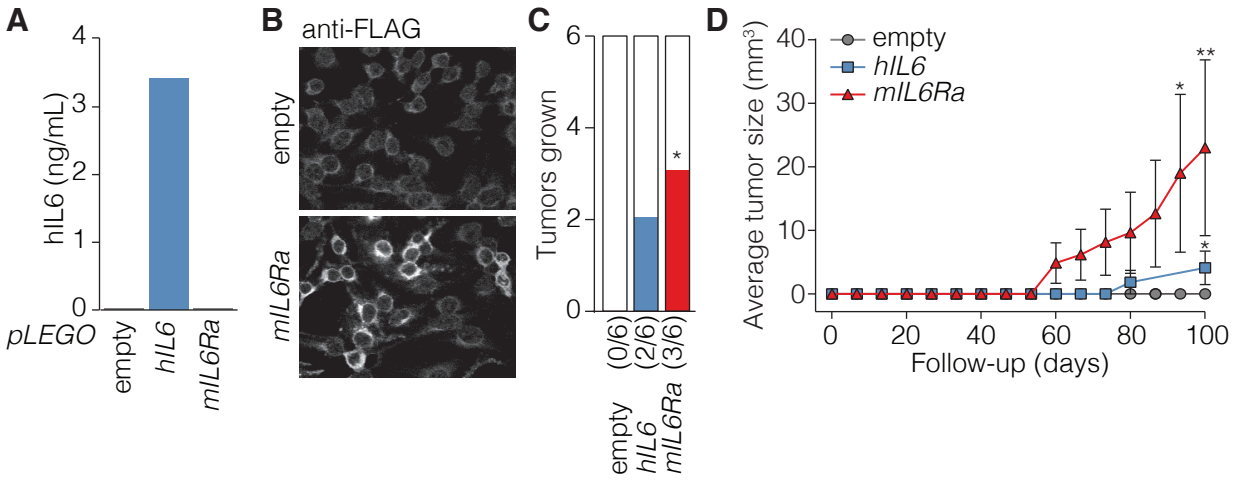


Fig. S11 IL-6 signaling drives clonogenicity *in vivo*. 031M cells transduced with empty *pLEGO-iV2* vector, *pLEGO-hIL6* or *pLEGO-mIL6Ra*. (*A*) Expression of (human) IL-6 ligand was verified by ELISA on supernatants from indicated cells. Detection was performed as for Fig. 2G. (*B*) Transduced cells were seeded on coverslips, and processed for immunofluorescence against the FLAG tag on the (mouse) mIL-6Ra receptor. (*C*) Immunodeficient mice were grafted with $5x10^5$ of indicated cells in Matrigel and growth was monitored over a period of 100 days. N=6 mice per group. Tumor take was observed in 3/6 mice injected with mIL6Ra receptor expressing cells (* P=0.0455 by χ^2 test), and 2/6 mice injected with hIL-6 ligand expressing cells. (*D*) Shown are average tumor sizes (and SEM) in time from experiment shown in panel *C*. * P<0.05, ** P<0.01 by T-test for indicated time points.

Table S1. List of antibodies and dilutions used.

Antibodies for immunofluorescence	Dilution	Clone number, manufacturer
Primary		
anti-α-SMA	1:100	ab5694, Abcam
anti-FLAG	1:500	clone M2, Sigma
Isotype control		
unconjugated IgG rabbit isotype	1:300	DA1E, Cell Signaling
Secondary		
Alexa Fluor 488 conjugated anti-rabbit IgG	1:400	A11008, Thermo Fisher
Antibodies for flow cytometry		
Primary		
FITC conjugated anti-HER2 Affibody	1:1500	N/A, Bromma, Sweden
anti-ERBB3	1:1500	SGP1, Abcam
PE conjugated anti-CD24	1:50	ML5, BD Biosciences
APC conjugated anti-CD29	1:50	MAR4, BD Biosciences
FITC conjugated anti-EPCAM	1:500	Ber-EP4, DAKO
anti-CXCR4	1:100	UMB2, Abcam
APC conjugated anti-CD44	1:50	G44-26, BD Biosciences
APC conjugated anti-CD133	1:25	AC133, MACS Miltenyibiotec
Biotin conjugated anti-LGR5	1:100	4D11F8, BD Biosciences
anti-Vimentin	1:100	0.N.602, Santa Cruz
Isotype controls		
Biotin conjugated LGR5 isotype Rat IgG2b	1:100	A95-1, BD Biosciences
PE conjugated IgG2a mouse isotype	1:50	G155-178, BD Biosciences
APC conjugated IgG2b mouse isotype	1:50	MPC-11, Biolegend
APC conjugated IgG1 mouse isotype	1:50	MOPC-21, BD Biosciences
FITC conjugated IgG1,K mouse isotype	1:200	P3.6.2.8.1, eBioscience
unconjugated IgG mouse isotype	1:100	X40, BD Biosciences
unconjugated IgG rabbit isotype	1:100	DA1E, Cell Signaling
Secondary antibodies/probes		
APC conjugated anti-mouse	1:800	550826, BD Biosciences
Alexa Fluor 488 conjugated anti-rabbit IgG	1:800	A-11008, Thermo Fisher
APC conjugated streptavidin	1:1000	17-4317-82, eBiosience
Reagents for cell sorting		
Primary antibodies/probes		
7-AAD	1:100	N/A, BD Biosciences
FITC conjugated anti-EPCAM	1:500	Ber-EP4, DAKO
Anti-EGFR	1:2000	H11, Dako
Secondary		
APC conjugated anti-mouse	1:800	550826, BD Biosciences
Antibodies for Western blot		
Primary		
anti-pSTAT3 (Tyr705)	1:1000	D3A7, Cell Signaling
anti-STAT3	1:1000	79D7, Cell Signaling
anti-GAPDH	1:5000	6C5, BioConnect
Secondary		
HRP-conjugated Goat anti rabbit	1:5000	7074, Cell Signaling
HRP-conjugated Goat anti mouse	1:5000	1031-05, Southern Biotech

Table S2. Primer sequences for quantitative RT-PCR**.**

Transcript	**Sequence**
GAPDH–forward:	5’-AATCCCATCACCATCTTCCA-3'
GAPDH–reverse:	5'-TGGACTCCACGACGTACTCA-3'
ZEB1–forward:	5′-GCACAAGAAGAGCCACAAGTA-3'
ZEB1–reverse:	5′-GCAAGACAAGTTCAAGGGTTC-3'
VIM–forward:	5′-CCCTCACCTGTGAAGTGGAT-3'
VIM–reverse:	5′-TCCAGCAGCTTCCTGTAGGT-3'
SNAI2–forward:	5′-GGTCAAGAAGCATTTCAACG-3'
SNAI2–reverse:	5′-CACAGTGATGGGGCTGTATG-3'
CDH2–forward:	5′-ACAGTGGCCACCTACAAAGG-3'
CDH2–reverse:	5′-CCGAGATGGGGTTGATAATG-3'
ERBB3–forward:	5’-TGGGGAACCTTGAGATTGTG-3'
ERBB3-reverse:	5’-GAGGTTGGGCAATGGTAGAG-3'
CDH1–forward:	5’-TGCCCAGAAAATGAAAAAGG-3'
CDH1–reverse:	5’-GTGTATGTGGCAATGCGTTC-3'
KRT19–forward:	5’-CCTGGAGTTCTCAATGGTGG -3'
KRT19–reverse:	5’-CTAGAGGTGAAGATCCGCGA -3'
CD44–forward:	5’-TGGAGCAAACACAACCTCTG-3'
CD44–reverse:	5’-CCACTTGGCTTTCTGTCCTC-3'
CD133–forward:	5’-TCCACAGAAATTTACCTACATTGG-3'
CD133–reverse:	5’-CAGCAGAGAGCAGATGACCA-3'
LGR5–forward:	5’-ACCAGACTATGCCTTTGGAAAC-3'
LGR5–reverse:	5’-TTCCCAGGGAGTGGATTCTAT-3'

REFERENCES FOR SUPPLEMENTARY FIGURES

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