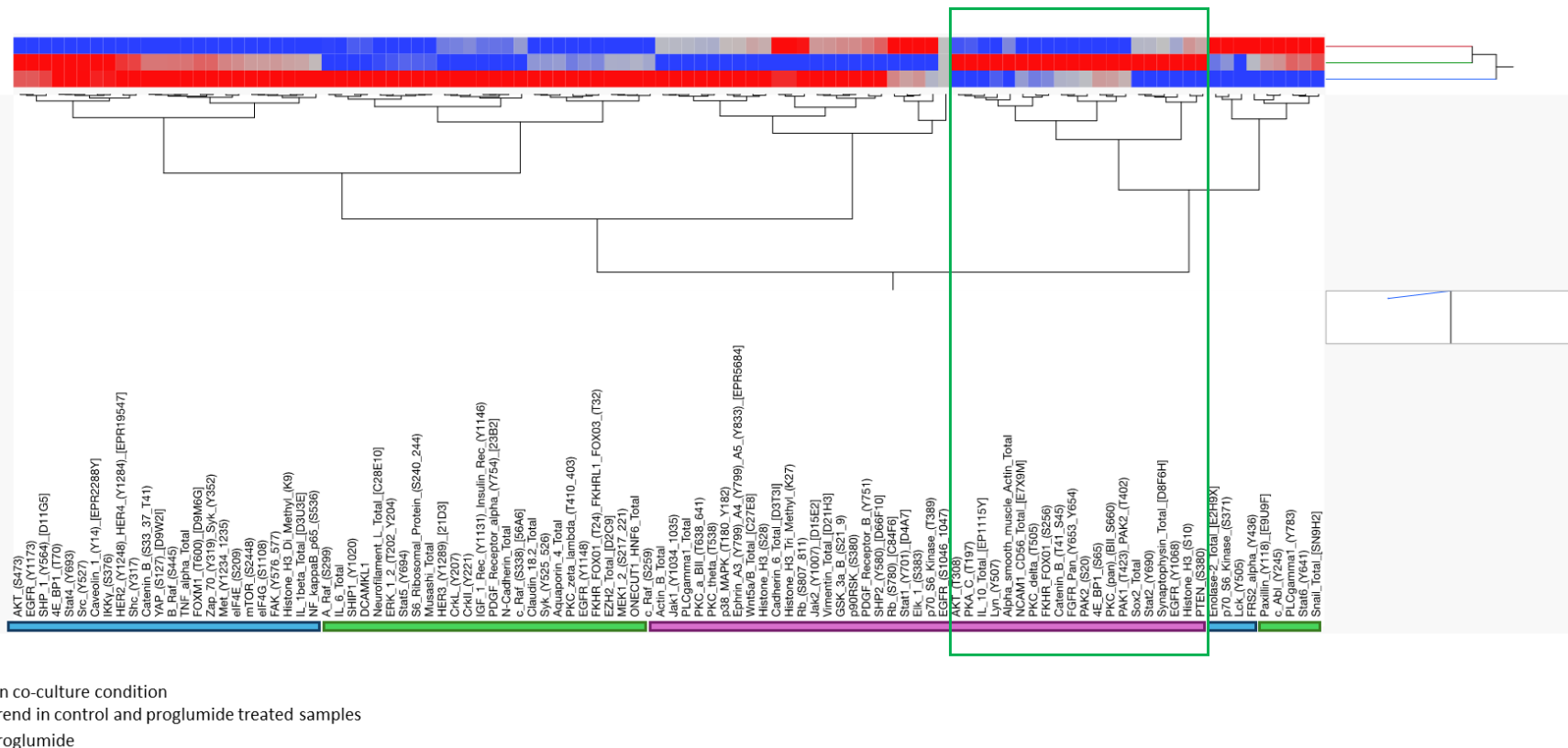
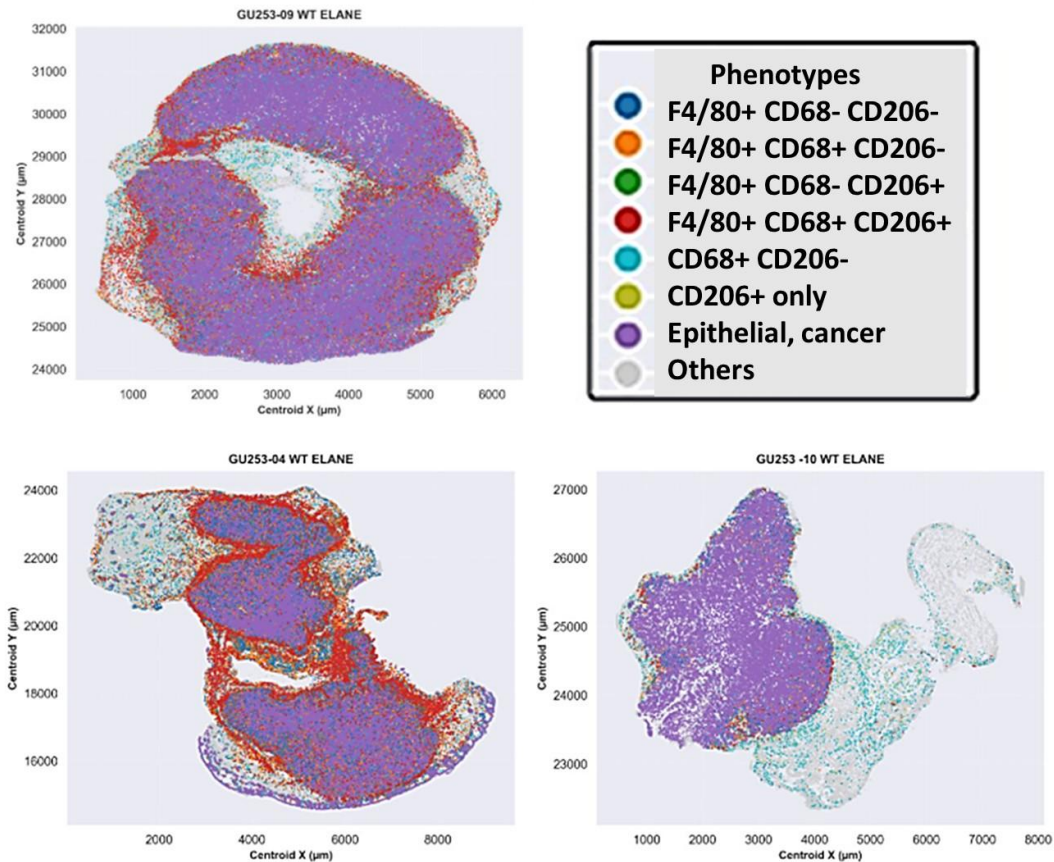


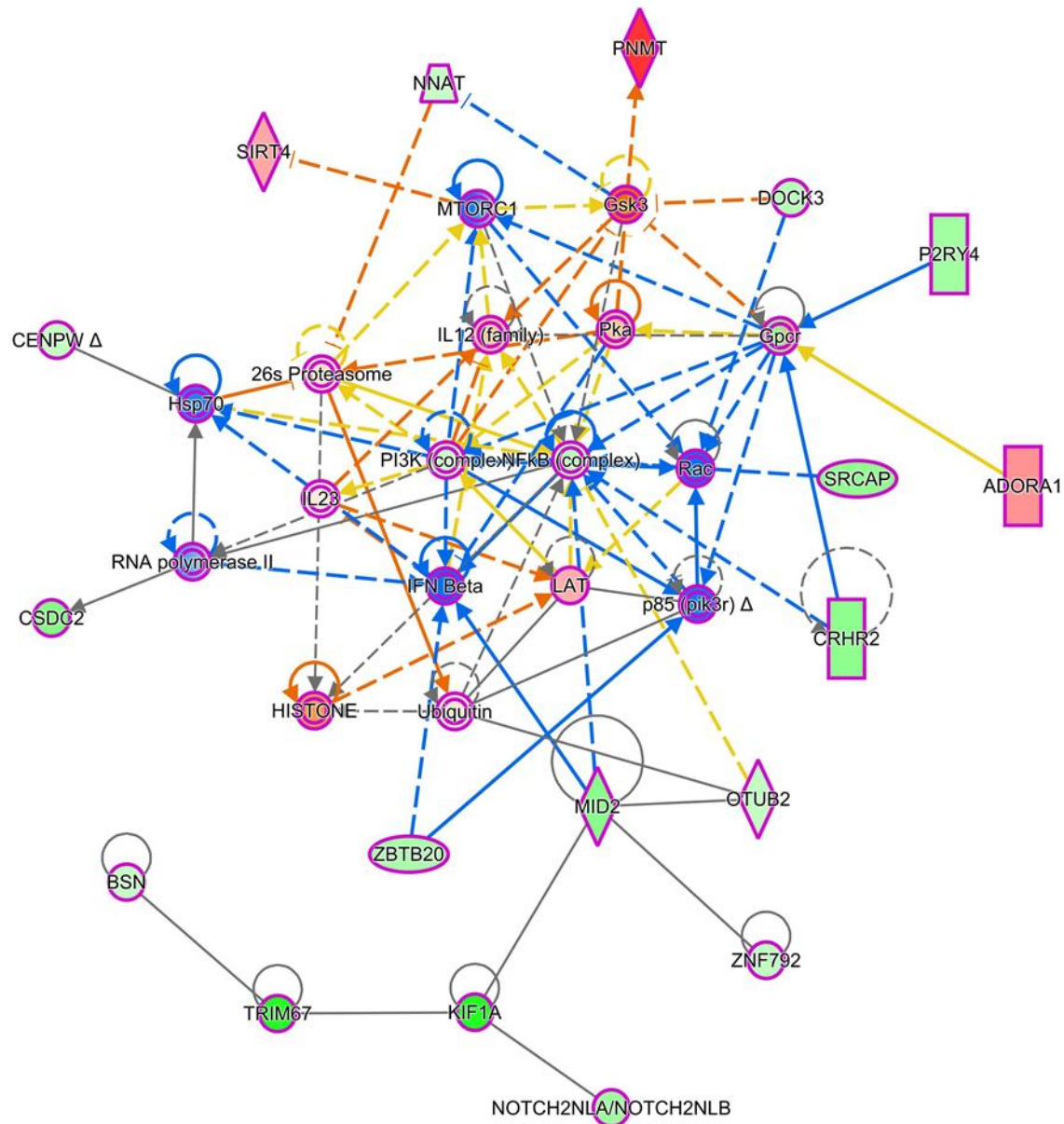
ASPC1 spheroids CTRL
 ASPC1 spheroids + U937
 ASPC1 spheroids + proglumide



Supplementary Fig S1. A complete unsupervised hierarchical clustering capturing the proteins changed when AsPC-1 spheroids were co-cultured with U937 cells or when treated with proglumide compared to untreated control spheroids is shown. The proteins outlines are magnified in Fig 2G.



Supplementary Fig S2. Spatial relationship of immune cells (macrophages) to human cancer epithelial cells in representative AsPC-1 wild-type tumors. Top right is the color scheme with the various antibodies.



Supplementary Fig S3. Genes identified by RNAseq in the NF κ B signaling pathway. NF κ B is the major mediator of inflammation. NF- κ B activation is associated with cancer cell proliferation, invasion, metastasis, and chemoresistance in pancreatic cancer. We also found that proglumide decreased NF κ B protein by RPPA in Spheroids and exosomes treated with proglumide. Genes that are downregulated in AsPC-1 spheroids by proglumide are outlined in purple. Graphics by the IPA software, Qiagen.

Gene name	Forward primer 5' to 3'	Reverse primer 5' to 3'
(Human)		
<i>SOCS-1</i>	TTCGCCCTTAGCGTGAAGATGG	TAGTGCTCCAGCAGCTCGAAGA
<i>ELANE</i>	TGCGCCCAACTTCGTCATGTCG	CGTAGCCGTTTTCGAAGATGCG
<i>GAPDH</i>	GTCTCCTCTGACTTCAACAGCG	ACCACCCTCTTGCTGTAGCCAA

Supplementary Table S1. Primer sequences for genes analyzed by qRT-PCR.

Surface Receptor Antibodies	Company	Cat# (clone)	Fluorophore	Link
CD206 (anti-human, M2 marker)	BioLegend	321109 (15-2)	APC	https://www.biolegend.com/en-us/products/apc-anti-human-cd206-mmr-antibody-2996
CD80 (anti-human,	BioLegend	375405 (W17149D)	FITC	https://www.biolegend.com/en-us/products/fitc-anti-human-cd80-antibody-20587
CD86 (anti-human)	BioLegend	374209 (BU63)	PE/Cy7	https://www.biolegend.com/en-us/products/pe-cyanine7-anti-human-cd86-antibody-15545
Cholecystokinin B receptor (human and mouse)	Abcam	Ab77077	Dy-Light 488-A	https://www.abcam.com/en-us/products/primary-antibodies/cck2-r-antibody-ab77077?srsId=AfmBOoquALudgTFuXdGC5GpXjy6_MSG8eKcNs9Do2iJ8Cyl8zLxvy0kw
CCR6 (anti-human CD196)	BioLegend	353407	BV-421-A	https://www.biolegend.com/de-de/products/brilliant-violet-421-anti-human-cd196-ccr6-antibody-7547
CCR2 (anti-human CD192)	BioLegend	357205	PE	https://www.biolegend.com/en-gb/products/pe-anti-human-cd192-ccr2-antibody-8529

Supplementary Table S2. Flow cytometry antibodies for cell surface receptor analysis for human immune cells and GPCR experiment

Antibody	Protein Nomenclature	Company	Cat #	Dilution	Host
4E-BP1 (S65)	4E_BP1_(S65)	CellSig	9451	1:50	R
4E-BP1 (T70)	4E_BP1_(T70)	CellSig	9455	1:200	R
A-Raf (S299)	A_Raf_(S299)	CellSig	4431	1:50	R
Actin, alpha smooth muscle	Alpha_smooth_muscle_Actin_Total	Abcam	ab5694	1:50	R
Actin, Beta	Actin_B_Total	CellSig	4967	1:200	R
AKT (S473) XP	AKT_(S473)	CellSig	4060	1:100	R
AKT (T308)	AKT_(T308)	CellSig	9275	1:100	R
Aquaporin_4	Aquaporin_4_Total	LS Bio	LS-C490149	1:200	R
B-Raf (S445)	B_Raf_(S445)	CellSig	2696	1:50	R
c-Abl (Y245)	c_Abl_(Y245)	CellSig	2861	1:100	R
c-Raf (S338) (56A6)	c_Raf_(S338)_[56A6]	CellSig	9427	1:200	RmAb
Cadherin 6 [D3T3I]	Cadherin_6_Total_[D3T3I]	CellSig	48111	1:50	R
Catenin (beta) (S33/37/T41)	Catenin_B_(S33_37_T41)	CellSig	9561	1:100	R
Catenin (beta) (T41/S45)	Catenin_B_(T41_S45)	CellSig	9565	1:50	R
Caveolin-1 (Y14) (EPR2288Y)	Caveolin_1_(Y14)_[EPR2288Y]	Epitomics	2267-1	1:200	RmAb
Claudin 18.2	Claudin_18.2_Total	Invitrogen	PA5-141108	1:500	R
CrkII (Y221)	CrkII_(Y221)	CellSig	3491	1:100	R
CrkL (Y207)	CrkL_(Y207)	CellSig	3181	1:100	R
DCLK1	DCAMKL1	Abcam	AB31704	1:200	R
EGFR (S1046/1047)	EGFR_(S1046_1047)	CellSig	2238	1:500	R
EGFR (Y1068)	EGFR_(Y1068)	CellSig	2234	1:50	R
EGFR (Y1148)	EGFR_(Y1148)	ThermoFish	44-792G	1:100	R
EGFR (Y1173)	EGFR_(Y1173)	ThermoFish	44-794G	1:100	R
eIF4E (S209)	eIF4E_(S209)	CellSig	9741	1:50	R
eIF4G (S1108)	eIF4G_(S1108)	CellSig	2441	1:1000	R
Elk-1 (S383)	Elk_1_(S383)	CellSig	9181	1:100	R
Enolase-2 (E2H9X) XP	Enolase-2_Total_[E2H9X]	CellSig	24330	1:100	RmAb
Ephrin A3 (Y799)/A4 (Y799)/A5 (Y833)	Ephrin_A3_(Y799)_A4_(Y799)_A5_(Y833)_[EPR5684]	Abcam	ab124881	1:100	RmAb
ErbB2/HER2(pY1248)-ErbB4/HER4(pY1284)	HER2_(Y1248)_HER4_(Y1284)_[EPR19547]	Abcam	ab201013	1:20,000	RmAb
ERK 1/2 (T202/Y204)	ERK_1_2_(T202_Y204)	CellSig	9101	1:1000	R
Ezh2 (D2C9) XP	EZH2_Total_[D2C9]	CellSig	5246	1:500	RmAb
FAK (Y576/577)	FAK_(Y576_577)	CellSig	3281	1:200	R
FGFR Pan (Y653/654)	FGFR_Pan_(Y653_Y654)	Invitrogen	PA5-64626	1:100	R
FKHR-FOX01 (S256)	FKHR_FOX01_(S256)	CellSig	9461	1:100	R
FKHR-FOX01 (T24)/FKHRL1-FOX03 (T32)	FKHR_FOX01_(T24)_FKHRL1_FOX03_(T32)	CellSig	9464	1:200	R
FOX01 (T600)	FOX01_(T600)_[D9M6G]	CellSig	14655	1:100	RmAb
FRS2-alpha (Y436)	FRS2_alpha_(Y436)	CellSig	3861	1:50	R

GSK-3a/B (S21/9)	GSK_3a_B_(S21_9)	CellSig	9331	1:100	R
HER3 (Y1289) (21D3)	HER3_(Y1289)_[21D3]	CellSig	4791	1:200	RmAb
Histone H3 (S10) Mitosis Marker	Histone_H3_(S10)	Upstate	06-570	1:200	R
Histone H3 (S28)	Histone_H3_(S28)	Upstate	07-145	1:1000	R
Histone H3, Di-Methyl (Lys9)	Histone_H3_Di_Methyl_(K9)	CellSig	9753	1:500	R
Histone H3, Tri-Methyl (Lys27)	Histone_H3_Tri_Methyl_(K27)	Millipore	07-449	1:2500	R
IGF-1 Rec (Y1131)/Insulin Rec (Y1146)	IGF_1_Rec_(Y1131)_ Insulin_Rec_(Y1146)	CellSig	3021	1:500	R
IKK γ (S376)	IKK γ _(S376)	CellSig	2689	1:50	R
IL-10	IL_10_Total_[EP1115Y]	Abcam	ab52909	1:2000	R
IL-1B (D3U3E)	IL_1beta_Total_[D3U3E]	CellSig	12703	1:100	RmAb
IL-6 (D5W4V) XP	IL_6_Total	CellSig	12912	1:50	RmAb
Jak1 (Y1034/1035)	Jak1_(Y1034_1035)	CellSig	3331	1:50	R
Jak2 (Y1007)	Jak2_(Y1007)_[D15E2]	CellSig	4406	1:200	RmAb
Lck (Y505)	Lck_(Y505)	ThermoFish	44-850G	1:50	R
Lyn (Y507)	Lyn_(Y507)	CellSig	2731	1:50	R
MEK1/2 (S217/221)	MEK1_2_(S217_221)	CellSig	9121	1:200	R
Met (Y1234/1235)	Met_(Y1234_1235)	CellSig	3126	1:200	R
mTOR (S2448)	mTOR_(S2448)	CellSig	2971	1:100	R
Musashi	Musashi_Total	CellSig	2154	1:50	R
N-Cadherin	N-Cadherin_Total	CellSig	4061	1:200	R
NCAM1 (CD56) (E7X9M)	NCAM1_CD56_Total_[E7X9M]	CellSig	3590	1:2000	R
Neutrophil Elastase	ELANE	OriGene	TA375845	1:100	R
Neurofilament-L (C28E10)	Neurofilament_L_Total_[C28E10]	CellSig	2837	1:100	R
NF-kappaB p65 (S536) (93H1)	NF_kappaB_p65_(S536)	CellSig	3033	1:200	RmAb
ONECUT1_HNF6	ONECUT1_HNF6_Total	LS Bio.	LS- C313311	1:200	R
p38 MAPK (T180/Y182)	p38_MAPK_(T180_Y182)	CellSig	9211	1:100	R
p70 S6 Kinase (S371)	p70_S6_Kinase_(S371)	CellSig	9208	1:50	R
p70 S6 Kinase (T389)	p70_S6_Kinase_(T389)	CellSig	9205	1:100	R
p90RSK (S380)	p90RSK_(S380)	CellSig	9341	1:200	R
PAK1 (T423)/PAK2 (T402)	PAK1_(T423)_PAK2_(T402)	CellSig	2601	1:100	R
PAK2 (S20)	PAK2_(S20)	CellSig	2607	1:100	R
PARP, cleaved (D214)	Paxillin_(Y118)_[E9U9F]	CellSig	9541	1:100	R
PDGF Receptor alpha (Y754) (23B2)	PDGF_Receptor_alpha _(Y754)_[23B2]	CellSig	2992	1:500	RmAb
PDGF Receptor beta (Y751)	PDGF_Receptor_B_(Y751)	CellSig	3161	1:50	R
PKA C (T197)	PKA_C_(T197)	CellSig	4781	1:200	R
PKC (pan) (betall S660)	PKC_(pan)_(BII_S660)	CellSig	9371	1:200	R
PKC α /BII (T638/641)	PKC_a_BII_(T638_641)	CellSig	9375	1:100	R

PKC delta (T505)	PKC_delta_(T505)	CellSig	9374	1:50	R
PKC theta (T538)	PKC_theta_(T538)	CellSig	9377	1:100	R
PKC zeta/lambda (T410/403)	PKC_zeta_lambda_(T410_403)	CellSig	9378	1:50	R
PLC-gamma-1	PLCgamma1_Total	CellSig	2822	1:500	R
PLCgamma1 (Y783)	PLCgamma1_(Y783)	CellSig	2821	1:100	R
PTEN (S380)	PTEN_(S380)	CellSig	9551	1:500	R
Raf (S259)	c_Raf_(S259)	CellSig	9421	1:100	R
Rb (S780)	Rb_(S780)_[C84F6]	CellSig	3590	1:2000	R
Rb (S807/811)	Rb_(S807_811)	CellSig	9308	1:200	R
S6 Ribosomal Protein (S240/244)	S6_Ribosomal_Protein_(S240_244)	CellSig	2215	1:1000	R
Shc (Y317)	Shc_(Y317)	CellSig	2431	1:100	R
SHIP1 (Y1020)	SHIP1_(Y1020)	CellSig	3941	1:50	R
SHP-1 (Y564) (D11G5)	SHP_1_(Y564)_[D11G5]	CellSig	8849	1:100	RmAb
SHP2 (Y580)	SHP2_(Y580)_[D66F10]	Biosource	44-558	1:500	R
Snail (SN9H2)	Snail_Total_[SN9H2]	CellSig	4719	1:2000	Rat
Sox2	Sox2_Total	CellSig	2748	1:100	R
Src (Y527)	Src_(Y527)	CellSig	2105	1:200	R
STAT1 (Y701) (D4A7)	Stat1_(Y701)_[D4A7]	CellSig	7649	1:100	RmAb
Stat2 (Y690)	Stat2_(Y690)	CellSig	4441	1:100	R
Stat4 (Y693)	Stat4_(Y693)	CellSig	5267	1:100	R
Stat5 (Y694)	Stat5_(Y694)	CellSig	9351	1:50	R
Stat6 (Y641)	Stat6_(Y641)	CellSig	9361	1:100	R
Syk (Y525/526)	Syk_(Y525_526)	CellSig	2711	1:50	R
Synaptophysin (D8F6H)	Synaptophysin_Total_[D8F6H]	CellSig	36406	1:100	RmAb
TNF alpha	TNF_alpha_Total	Abcam	ab9635	1:200	R
Vimentin (D21H3)	Vimentin_Total_[D21H3]	CellSig	5741	1:200	RmAb
Wnt5a/B (C27E8)	Wnt5a/B_Total_[C27E8]	CellSig	2530	1:100	RmAb
YAP (S127) (D9W2I)	YAP_(S127)_[D9W2I]	CellSig	13008	1:100	RmAb
Zap-70 (Y319)/Syk (Y352)	Zap_70_(Y319)_Syk_(Y352)	CellSig	2701	1:400	R
R: rabbit polyclonal; RmAb: rabbit monoclonal					

Supplementary Table S3. Antibody list for RPPA

Name	Company	Cat#	Link
AKT T308	Cell signaling	9275S	https://www.cellsignal.com/products/primary-antibodies/phospho-akt-thr308-antibody/9275
PKC delta T505	Cell signaling	9374S	https://www.cellsignal.com/products/primary-antibodies/phospho-pkcd-thr505-antibody/9374
SOX2	Cell signaling	2748S	https://www.cellsignal.com/products/primary-antibodies/sox2-antibody/2748
GAPDH	Cell signaling	5174S	https://www.cellsignal.com/products/primary-antibodies/gapdh-d16h11-xp-rabbit-mab/5174

Supplementary Table S4: Antibodies used for western blot. All antibodies were used at a titer of 1:1000.

Anti- <i>ELANE</i> shRNA number	Catalogue # OriGene (TL313237V)	Target sequences (5' to 3')
shRNA-A	TI352941	GGCTAATCCACGGAATTGCCTCCTTCGTC
shRNA-B	TI352942	GCACTGCGTGGCGAATGTAAACGTCCGCG
shRNA-C	TI352943	CGACTCTATCATCCAACGCTCCGAGGACA
Scrambled control	TR30012	GCACTACCAGAGCTAACTCAGATAGTACT

Supplementary Table S5: Anti-human *ELANE* shRNA constructs used from OriGene with catalogue number and target sequences provided. The link for the website:

<https://www.origene.com/catalog/rnai/shrna-lentiviral-particles/tl313237v-neutrophil-elastase-elane-human-shrna-lentiviral-particle-locus-id-1991>

Target	Species	Company	Cat#	Titer	Reporter
Arginase 1	Anti-mouse	ThermoFisher	PA5-29645	1:1,800	
iNOS	Anti-mouse	Abcam	Ab15323	1:60	
Ki67	Anti-mouse	BioCare medical	CRM 325	1:80	
FasR	Anti-mouse	ThermoFisher	PA5-79236	1.25µg/ml	
CD68	Anti-mouse	Akoya Bioscience	BX015; Clone: AKYP0142	1:200	Alexa Fluor 647-RX015
Pan-CK	Anti-Human	Akoya Bioscience	BX066 Clone: AKYP0053	1:200	Alexa Fluor 750-RX066
CD206	Anti-mouse	Akoya Bioscience	BX016 Clone: AKYP0137	1:200	Alexa-Fluor 647-RX016
F4/80	Anti-mouse	Akoya Bioscience	BX006 Clone: AKYP0135	1:200	Alexa Fluor 647-RX006

Supplementary Table S6: Antibodies used for Immunohistochemistry of tumors

Antibodies for flow cytometry with ASPC1 wt/ELANE ko tumors					
		Company	Cat#	fluro	link
surface antibody	CD45	Biolengend	103151	BV650	https://www.biolegend.com/en-us/products/brilliant-violet-650-anti-mouse-cd45-antibody-11987
	Ly6G	Biolengend	127623	APC/Cyanine7	https://www.biolegend.com/en-us/products/apc-cyanine7-anti-mouse-ly-6g-antibody-6755
	CD86	Biolengend	105061	Spark PLUS B550	https://www.biolegend.com/en-us/products/spark-plus-b550-anti-mouse-cd86-antibody-25860
	CD206	Biolengend	141717	BV421	https://www.biolegend.com/en-us/products/brilliant-violet-421-anti-mouse-cd206-mmr-antibody-8638
	F4/80	Biolengend	123113	PE/Cyanine7	https://www.biolegend.com/en-us/products/pe-cyanine7-anti-mouse-f4-80-antibody-4070
	I-A/I-E (MHC ClassII)	Biolengend	107625	PerCP/Cyanine5.5	https://www.biolegend.com/en-us/products/percp-cyanine5-5-anti-mouse-i-a-i-e-antibody-4282
		Biolengend	107621	Alexa Fluor® 700	https://www.biolegend.com/en-us/products/alexa-fluor-700-anti-mouse-i-a-i-e-antibody-3413
Introcellular antibody	Arginase	invitrogen	12-3697-82	PE	https://www.thermofisher.com/antibody/product/Arginase-1-Antibody-clone-A1exF5-Monoclonal/12-3697-82
	CD68	Biolengend	137027	Pacific Blue	https://www.biolegend.com/en-us/products/pacific-blue-anti-mouse-cd68-antibody-16785

Supplementary Table S7. Antibodies for flow cytometry to analyze immune cells in tumors.

Actin_B_Total	AKT_(T308)	A_Raf_(S299)	Cadherin_6_Total_[D3T3I]	Catenin_B_(S33_37_T41)	Catenin_B_(T41_S45)
56387.31949	7700.190583	6317.004507	3644.593857	18287.99531	1017.394464
64860.87846	7631.193853	7442.781845	3551.055601	19633.65037	2960.164235
49020.81049	8821.966101	6304.378025	2081.824172	19302.69554	5670.313289
Enolase-2_Total_[E2H9X]	EZH2_Total_[D2C9]	FGFR_Pan_(Y653_Y654)	FRS2_alpha_(Y436)	Histone_H3_Tri_Methyl_(H3K9me3)	Jak1_(Y1034_1035)
11441.47588	27722.49738	15677.78228	11637.64598	14414.64833	57526.44523
10036.6608	38177.44559	16219.99865	9759.533394	14371.46546	68871.68009
10270.18653	31888.47332	16932.67499	10625.37097	13711.63502	48050.11141
mTOR_(S2448)	NCAM1_CD56_Total_[E7X9]	Neurofilament_L_Total_[C28E10]	p38_MAPK_(T180_Y182)	Rb_(S780)_[C84F6]	Sox2_Total
24834.76799	136.728912	10540.70317	7974.467913	34544.36812	16366.63465
34891.55278	166.5007429	11498.82783	11568.02316	31257.05474	15851.18479
31257.05474	231.8290158	10572.37551	4023.873161	23155.79126	17017.53609
Stat5_(Y694)	Synaptophysin_Total_[D8F6]	Vimentin_Total_[D21H3]	4E_BP1_(S65)	4E_BP1_(T70)	B_Raf_(S445)
30333.24834	15184.04158	25848.29312	6142.576587	92966.97303	24587.65229
38948.66184	14898.26744	32859.61314	9720.576051	98715.77101	32532.67811
31257.05474	15475.29736	11849.01611	11754.59775	98715.77101	30638.10957
EGFR_(S1046_1047)	EGFR_(Y1173)	HER2_(Y1248)_HER4_(Y1284)_[EPR19547]	ERK_1_2_(T202_Y204)	FAK_(Y576_577)	GSK_3a_B_(S21_9)
4.54E-05	13293.09339	4774.286023	4264.157071	18826.11747	11170.14752
4.54E-05	18620.1532	7738.788835	6087.542496	24100.79611	11637.64598
4.54E-05	19692.62609	7495.063864	4385.240194	22247.84055	10086.97093
Histone_H3_(S10)	NF_kappaB_p65_(S536)	PAK1_(T423)_PAK2_(T402)	Paxillin_(Y118)_[E9U9F]	PKC_(pan)_(BII_S660)	PKC_a_BII_(T638_641)
11872.73614	5426.230522	4332.931426	9518.573287	6136.440452	40134.85274
10107.16359	9566.286429	6721.050363	8690.621154	11614.38455	55826.29674
12771.86423	7615.947822	8586.956208	9218.795887	14913.16497	29143.86577
PKC_zeta_lambda_(T410_403)	PLCgamma1_(Y783)	S6_Ribosomal_Protein_(S240_244)	SHIP1_(Y1020)	Stat6_(Y641)	Wnt5a/B_Total_[C27E8]
9072.470759	9575.85224	39340.1114	43914.48857	9749.784095	30946.03477
11568.02316	8233.774323	56387.31949	92042.00291	6081.461337	32859.61314
9537.628101	9320.768332	40945.61024	39735.49519	8910.630374	28001.11952
DCAMKL1	Aquaporin_4_Total	ONECUT1_HNF6_Total			
41772.78556	40134.85274	34200.63809			
47098.67881	52052.06032	40945.61024			
41357.12993	43914.48857	37049.14145			

Supplementary Table S8. RPPA raw data