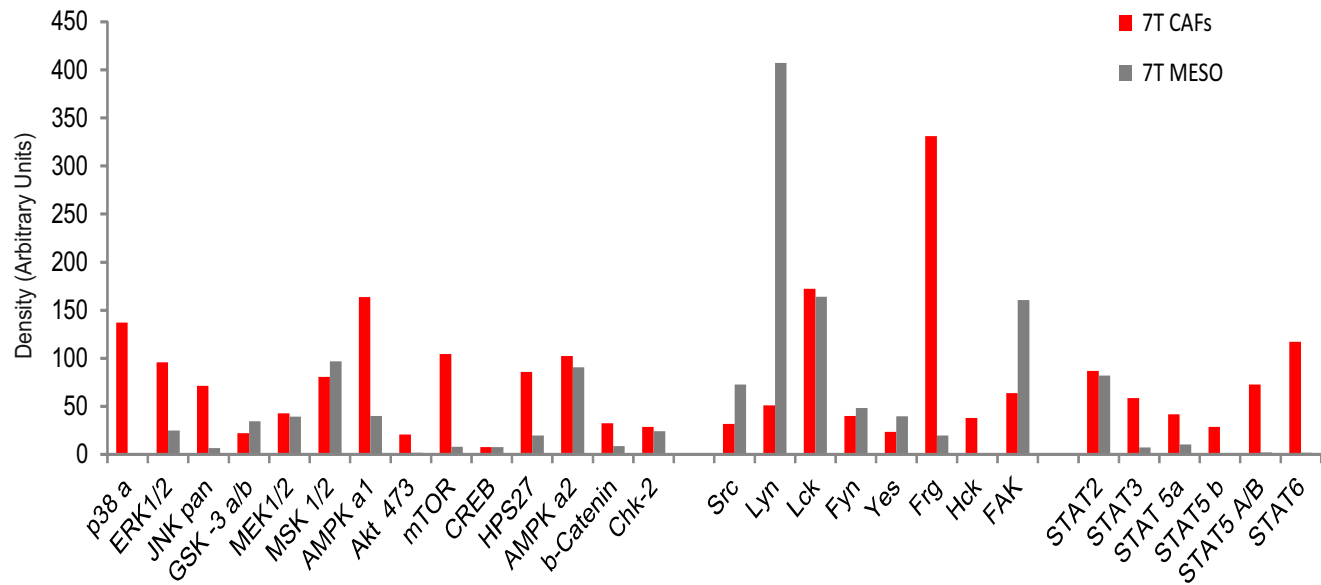
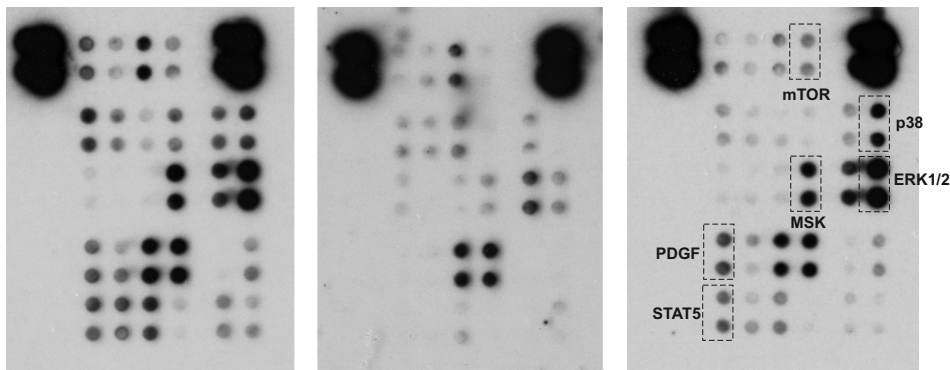


Whole tumour 7T

Mesothelial 7T

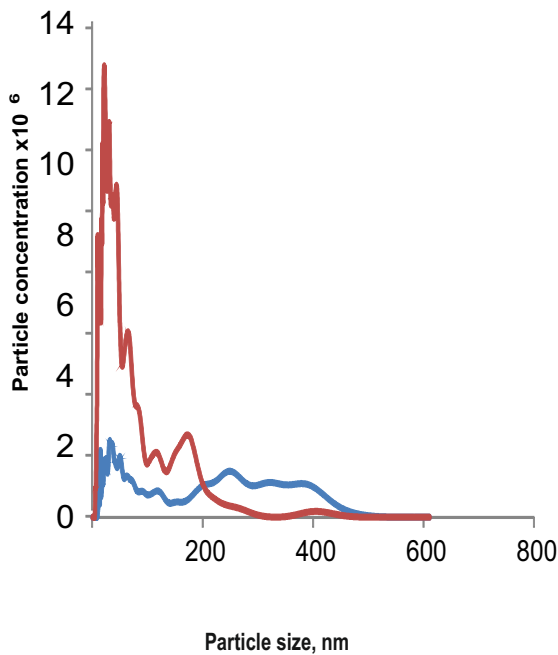
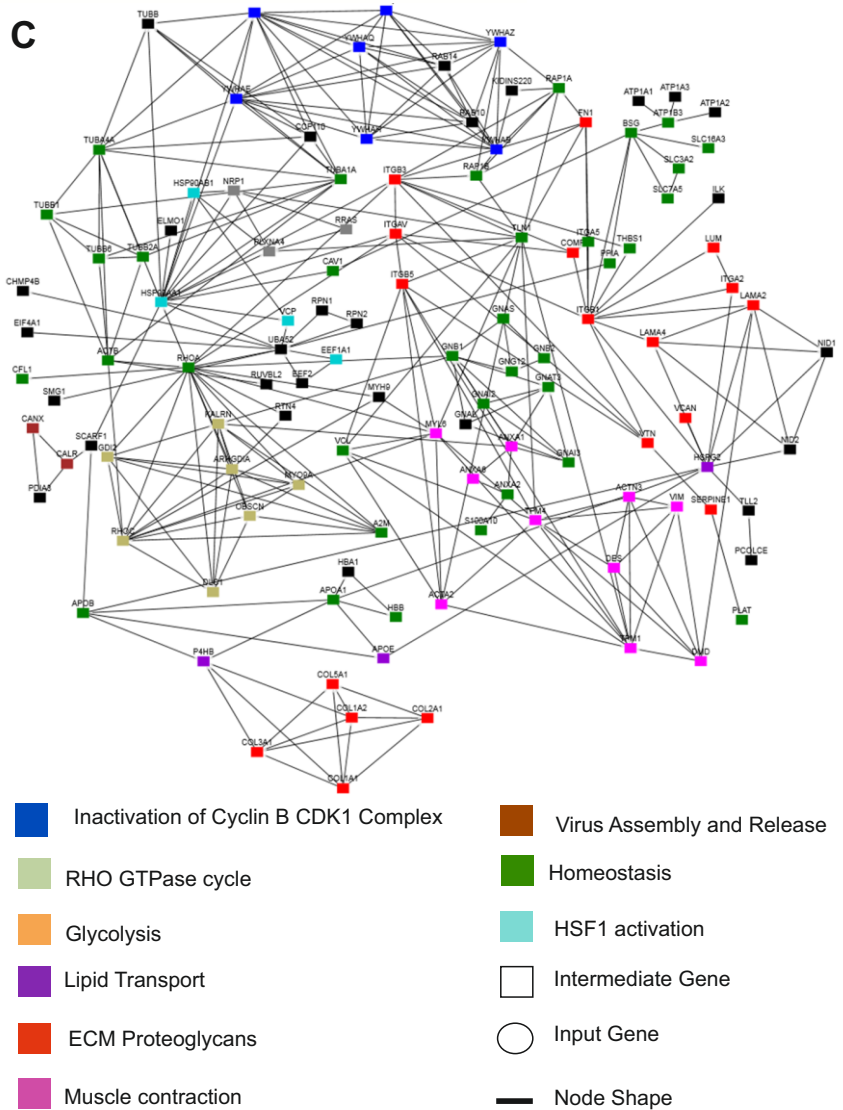
CAFs 7T



**Supplemental Figure S1.** Differential contribution of tumour cells and CAFs to activation of signalling pathways in the whole tumour. **A.** The image shows the immunoblots of kinases in whole mesothelioma tumour 7T tissue (left), in primary mesothelial (mesothelioma) cells derived from tumour 7T (middle) and in CAFs derived from tumour 7T (right). Signals from the most differentially activated kinases are boxed. **B.** Kinase phosphorylation status in 7T CAFs and 7T Mesothelioma cells quantified by densitometry.

**A**

File Edit View Experiment Export Quant Window Help									
Protein Threshold: 90.0% Min # Peptides: 2 Peptide Threshold: 95%									
Display Options: Total Spectrum Count Req Mods: No Filter Search:									
<div> <div>Load Data</div> <div>Samples</div> <div>Proteins</div> <div>Similarity</div> <div>Quantify</div> <div>Publish</div> <div>Statistics</div> </div>									
<div> <div>Probability Legend:</div> <div> <div>over 95%</div> <div>80% to 94%</div> <div>50% to 79%</div> <div>20% to 49%</div> <div>0% to 19%</div> </div> </div>									
<div> <div>Bio View:</div> <div>363 Proteins in 296 Clusters</div> <div>With 303 HIDDEN</div> </div>									
1	✓	Cluster of Dystrophin OS=Homo sapiens GN=DMD PE=1 SV=2 (DMD_HUMAN)	DMD_HUMAN	427kDa	13	2	0	1	
2	✓	Cluster of Centriolin OS=Homo sapiens GN=CEP110 PE=1 SV=2 (CEP110_HUMAN)	CEP110_HUMAN	269kDa	10	2	0	0	
3	✓	Ankyrin-3 OS=Homo sapiens GN=ANK3 PE=1 SV=3	ANK3_HUMAN	480kDa	4	1	0	0	
4	✓	Cluster of Isoform 4 of Microtubule-actin cross-linking factor 1, isoforms 1/2/3/5 OS=Homo sapiens GN=HACF1 (Q9UPH3-5)	Q9UPH3-5	?	17	5	0	0	
5	✓	Cluster of Bullous pemphigoid antigen 1, isoforms 1/2/3/4/5/8 (Fragment) OS=Homo sapiens GN=DST PE=1 SV=3 (BPAL1_HUMAN)	BPAL1_HUMAN	372kDa	13	7	0	7	
6	✓	Fibrous sheath-interacting protein 2 OS=Homo sapiens GN=FSIP2 PE=1 SV=3	FSIP2_HUMAN	370kDa	5	2	1	0	
7	✓	Isoform 6 of Titin OS=Homo sapiens GN=TTN	Q8WZ42-6	?	4	1	1	0	
8	✓	Dynein heavy chain 9, axonemal OS=Homo sapiens GN=DNAH9 PE=1 SV=2	DNAH9_HUMAN	512kDa	7	0	1	0	
9	✓	Cluster of Serine/arginine repetitive matrix protein 2 OS=Homo sapiens GN=SRRM2 PE=1 SV=2 (SRRM2_HUMAN)	SRRM2_HUMAN	300kDa	7	0	1	0	
10	✓	Ryanodine receptor 1 OS=Homo sapiens GN=RYR1 PE=1 SV=3	RYR1_HUMAN	565kDa	2	2	1	0	
11	✓	Cluster of Golgin subfamily A member 4 OS=Homo sapiens GN=GOLGA4 PE=1 SV=1 (GOLGA4_HUMAN)	GOLGA4_HUMAN	261kDa	4	2	2	0	
12	✓	Cluster of Isoform 3 of Histone-lysine N-methyltransferase MLL2 OS=Homo sapiens GN=MLL2 (O14686-3)	O14686-3	?	8	4	2	0	
13	✓	Cluster of Collagen alpha-3(VI) chain OS=Homo sapiens GN=COL6A3 PE=1 SV=4 (COL6A3_HUMAN)	COL6A3_HUMAN	244kDa	6	8	3	4	
14	✓	Cluster of Isoform 3 of Hyaluronan OS=Homo sapiens GN=PD401P (Q5VU43-3)	Q5VU43-3	?	16	0	4	0	
15	✓	Glia-derived nexin OS=Homo sapiens GN=SERPINE2 PE=1 SV=1	GDM_HUMAN	44kDa	8	6	4	4	
16	✓	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1 OS=Homo sapiens GN=RP11 PE=1 SV=1	RP11_HUMAN	69kDa	1	3	5	6	
17	✓	Cluster of Proteasome subunit alpha type-7 OS=Homo sapiens GN=PSMA7 PE=1 SV=1 (PSMA7_HUMAN)	PSMA7_HUMAN	28kDa	1	6	2	2	
18	✓	Centrosome-associated protein 350 OS=Homo sapiens GN=CP350 PE=1 SV=1	CP350_HUMAN	351kDa	1	0	7	3	
19	✓	Myristoylated alanine-rich C-kinase substrate OS=Homo sapiens GN=MARCKS PE=1 SV=4	MARCKS_HUMAN	32kDa	16	11	7	6	
20	✓	Transitional endoplasmic reticulum ATPase OS=Homo sapiens GN=VCP PE=1 SV=4	TERA_HUMAN	89kDa	19	20	12	12	
21	✓	Cytoskeleton-associated protein 4 OS=Homo sapiens GN=CKAP4 PE=1 SV=2	CKAP4_HUMAN	66kDa	3	5	12	12	
22	✓	Integrin beta-1 OS=Homo sapiens GN=ITGB1 PE=1 SV=2	ITB1_HUMAN	88kDa	9	9	13	10	
23	✓	Cluster of Isoform 5 of Obscurin OS=Homo sapiens GN=OBSN (Q5VST9-6)	Q5VST9-6	?	20	25	15	11	
24	✓	Cluster of Clathrin heavy chain 2 OS=Homo sapiens GN=CLTC1 PE=1 SV=2 (CLH2_HUMAN)	CLH2_HUMAN	187kDa	2	14	15	13	
25	✓	Pigment epithelium-derived factor OS=Homo sapiens GN=SERPINF1 PE=1 SV=3	PEDF_HUMAN	46kDa	12	12	17	20	
26	✓	Cluster of Hyalofin OS=Homo sapiens GN=HYOF PE=1 SV=1 (HYOF_HUMAN)	HYOF_HUMAN	233kDa	4	8	24	28	
27	✓	Cluster of Tenascin-X OS=Homo sapiens GN=TNXB PE=1 SV=3 (TNXB_HUMAN)	TNXB_HUMAN	464kDa	0	0	25	41	
28	✓	Cluster of Peroxiredoxin-1 OS=Homo sapiens GN=PRDX1 PE=1 SV=1 (PRDX1_HUMAN)	PRDX1_HUMAN	22kDa	13	24	25	32	
29	✓	Vinculin OS=Homo sapiens GN=VCL PE=1 SV=4	VINC_HUMAN	124kDa	10	22	26	31	
30	✓	Glyceraldehyde-3-phosphate dehydrogenase OS=Homo sapiens GN=GAPDH PE=1 SV=3	G3P_HUMAN	36kDa	25	48	27	24	
31	✓	Basement membrane-specific heparan sulfate proteoglycan core protein OS=Homo sapiens GN=HSPG2 PE=1 SV=3	PGC4_HUMAN	469kDa	23	15	15	13	
32	✓	Cluster of Alpha-2-macroglobulin OS=Homo sapiens GN=A2M PE=1 SV=2 (A2MG_HUMAN)	A2MG_HUMAN	163kDa	18	20	34	35	
33	✓	Annexin A6 OS=Homo sapiens GN=ANXA6 PE=1 SV=3	ANXA6_HUMAN	76kDa	24	26	35	31	
34	✓	Annexin A1 OS=Homo sapiens GN=ANXA1 PE=1 SV=2	ANXA1_HUMAN	39kDa	20	16	36	27	
35	✓	Annexin A5 OS=Homo sapiens GN=ANXA5 PE=1 SV=2	ANXA5_HUMAN	36kDa	18	15	41	29	
36	✓	Cluster of Moesin OS=Homo sapiens GN=MSN PE=1 SV=3 (MOES_HUMAN)	MOES_HUMAN	68kDa	27	30	42	40	
37	✓	Cluster of 14-3-3 protein zeta/delta OS=Homo sapiens GN=VWHAZ PE=1 SV=1 (14332_HUMAN)	14332_HUMAN	28kDa	17	9	42	29	
38	✓	Cluster of L-lactate dehydrogenase A chain OS=Homo sapiens GN=LDHA PE=1 SV=2 (LDHA_HUMAN)	LDHA_HUMAN	37kDa	12	14	44	23	
39	✓	Cluster of Heat shock protein HSP 90-beta OS=Homo sapiens GN=HSP90AB1 PE=1 SV=4 (HSP90B_HUMAN)	HSP90B_HUMAN	83kDa	124	145	105	104	
40	✓	Cluster of Keratin, type I cytoskeletal 10 OS=Homo sapiens GN=KRT10 PE=1 SV=6 (KIC10_HUMAN)	KIC10_HUMAN	59kDa	78	82	122	104	

**B****C**

**Supplemental Figure S2.** Changes in CAF-EVs protein content by CAF treatment with Simvastatin.

**A.** An extract from the Mass Spectrometry results showing the EV proteins with a changed concentration (reduced or increased) after treatment of CAFs with Simvastatin. **B.** Conditioned medium from activated macrophages increases production of EVs by CAFs. EV-depleted conditioned media (10 ml) from THP-1 cells stimulated with 10  $\mu$ g/ml LPS was added to cultured CAFs 24 h prior to EV collection. CAF-EVs were quantified by nanoparticle tracking analysis (NTA). **C.** Differentially present proteins in EVs from Simvastatin-treated and untreated CAFs form a network of the pathways related to cell cycle, metabolism, growth factors, integrins, homeostasis and lipid transport.

**Table S1. Top down-regulated genes (Database REACTOME)**

#	Gene	P-value FDR	Network Model CytoScape
1	<a href="#">CTNB1_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
2	<a href="#">PSA7_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
3	<a href="#">RAN_HUMAN</a>	~ 0.000961538 (0.0001)	<a href="#">view</a>
4	<a href="#">RL40_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
5	<a href="#">U520_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
6	<a href="#">HSP7C_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
7	<a href="#">TERA_HUMAN</a>	~ 0.000961538 (0.0001)	<a href="#">view</a>
8	<a href="#">GELS_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
9	<a href="#">RS3_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
10	<a href="#">HSPB1_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
11	<a href="#">RPN1_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
12	<a href="#">IF2B_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
13	<a href="#">EIF3I_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
14	<a href="#">IF4A2_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
15	<a href="#">CDC26_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
16	<a href="#">RLA2_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
17	<a href="#">HSP71_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
18	<a href="#">RPN2_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
19	<a href="#">VIME_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
20	<a href="#">CHM4B_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
21	<a href="#">ATPB_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
22	<a href="#">EF1A1_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
23	<a href="#">PTRF_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
24	<a href="#">PRIC1_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>
25	<a href="#">IF4A1_HUMAN</a>	< 0.000961538 (0.0001)	<a href="#">view</a>

**Table S2. Top down-regulated genes (Data base INTACT)**

#	Gene	P-value FDR	Network Model CytoScape
1	<a href="#">THIO_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
2	<a href="#">PRDX6_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
3	<a href="#">PGBM_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
4	<a href="#">K2C1B_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
5	<a href="#">GBB1_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
6	<a href="#">K1C16_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
7	<a href="#">S10AA_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
8	<a href="#">PSA7_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
9	<a href="#">H90B2_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
10	<a href="#">HSP7C_HUMAN</a>	~ 0.000213904 (0.0001)	<a href="#">view</a>
11	<a href="#">HS902_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
12	<a href="#">AHNK_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
13	<a href="#">TMEDA_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
14	<a href="#">K2C1_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
15	<a href="#">ALDOA_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
16	<a href="#">ITB1_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
17	<a href="#">RS3_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
18	<a href="#">HSPB1_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
19	<a href="#">GBG12_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
20	<a href="#">PPIB_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
21	<a href="#">RHOC_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
22	<a href="#">TSP1_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
23	<a href="#">CALR_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
24	<a href="#">FKB1A_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
25	<a href="#">RPN1_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
26	<a href="#">RAC2_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
27	<a href="#">EIF3I_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
28	<a href="#">GDIB_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
29	<a href="#">RAB1B_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>
30	<a href="#">APOE_HUMAN</a>	< 0.000213904 (0.0001)	<a href="#">view</a>