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Name	Mechanism	Concentration range	Supplier
DMSO	Vehicle control		Sigma-Aldrich
Trametinib	Inhibit MEK	30nM to 10µM	LC Laboratories
Ceritinib	Inhibit ALK tyrosine kinases, IGF1R, IR and STK22D	30nM to 10µM	LC Laboratories
Dabrafenib	Inhibit BRAFVEOOE	30nM to 10µM	LC Laboratories
6-Diazo-5-oxo-L- norleucine (DON)	Inhibit glutaminases	30nM to 10µM	Sigma-Aldrich
V9302	Inhibit transmembrane glutamine flux	30nM to 10µM	MedChemExpress
EHT1864	Inhibit Rac family small GTPases	30nM to 10µM	Tocris
BPTES	Inhibit glutaminase	30nM to 10µM	MedChemExpress
Imatinib	Inhibit Bcr-Abl tyrosine kinase; decrease hexokinase and G6PD activity	30nM to 10µM	LC Laboratories
2-Deoxy-D-glucose (2DG)	Suppress glycolysis by inhibiting hexokinase	30nM to 12µM	Sigma-Aldrich
Lonidamine	Suppress glycolysis by inhibiting hexokinase, mitochondrial pyruvate carrier and plasma membrane monocarboxylate transporters	30nM to 12µM	Sigma-Aldrich
Oxythiamine	Suppress PPP by inhibiting transketolase	30nM to 12µM	Sigma-Aldrich
3-Bromopyruvate (3BP)	Suppress glycolysis by inhibiting hexokinase	30nM to 12µM	Sigma-Aldrich
pan-RAS-in-1	Inhibit Pan-RAS	30nM to 10µM	MedChemExpress
Linsitinib	Inhibit IGF1R and IR	30nM to 10µM	MedChemExpress
Metformin	Activate AMPK	30nM to 12µM	MedChemExpress
Phenformin	Activate AMPK	30nM to 12µM	Sigma-Aldrich
AXL1717	Inhibit IGF1R	30nM to 10µM	MedChemExpress
EIPA	Inhibit macropinocytosis	50µM or 100µM	Sigma-Aldrich
Fucoidan	Block receptor-mediated albumin endocytosis	200ng/ml	Sigma-Aldrich
Pralsetinib	Inhibit RET	50nM	MedChemExpress
Serabelisib	Inhibit PI3Ka	ЗµМ	MedChemExpress
Alpelisib	Inhibit PI3Ka	ЗμМ	MedChemExpress

Gene Set	Description	ER	p-value	FDR	userID
hsa05161	Hepatitis B	2.85727833	3.51E-04	0.11225006	CDK2;CDK6;IFNA8;JAK1;JUN;LAMTOR5;MAP2K4; MAPK9;PTK2B;SMAD4;TGFBR1;TICAM1;VDAC3;Y WHAB
hsa04115	p53 signaling pathway	3.64622832	7.06E-04	0.11295613	ATM;CDK2;CDK6;CHEK1;CHEK2;MDM4;PMAIP1;R RM2B;SESN3
hsa04110	Cell cycle	2.64235031	0.00281872	0.27150199	ATM;CDC27;CDK2;CDK6;CDKN1C;CHEK1;CHEK2;R BL1;SMAD4;YWHAB;YWHAH
hsa05203	Viral carcinogenesis	2.35249249	0.00339377	0.27150199	CDK2;CDK6;CHEK1;HDAC9;HLA- E;JAK1;JUN;PMAIP1;RBL1;REL;VDAC3;YWHAB;YW HAH
hsa04520	Adherens junction	3.33349139	0.0046154	0.29538586	CSNK2B;FGFR1;IGF1R;INSR;SMAD4;TGFBR1;YES1
hsa04910	Insulin signaling pathway	2.51334668	0.00618735	0.31750736	CALM2;CBL;INSR;MAPK9;PHKA1;PHKG2;PRKAR2B ;PRKCI;RHOQ;TSC1
hsa04218	Cellular senescence	2.24641193	0.00694547	0.31750736	ATM;CALM2;CDK2;CDK6;CHEK1;CHEK2;HLA- E;PPID;RBL1;TGFBR1;TSC1;VDAC3
hsa04068	FoxO signaling pathway	2.3003512	0.01132681	0.45307223	ATM;CDK2;FOXG1;IGF1R;INSR;MAPK9;PLK4;SGK3; SMAD4;TGFBR1
hsa04217	Necroptosis	2.22492985	0.0141079	0.50161406	CHMP6;GLUD2;IFNA8;JAK1;JMJD7- PLA2G4B;MAPK9;PPID;RBCK1;TICAM1;VDAC3
hsa04014	Ras signaling pathway	1.75559141	0.03380209	0.76877909	CALM2;FGFR1;IGF1R;INSR;JMJD7- PLA2G4B;KIT;MAPK9;NF1;PLA2G10;PLA2G12A;PL CE1;RASGRP4;REL
hsa03440	Homologous recombination	3.19342872	0.03499651	0.76877909	ATM;BABAM2;RAD52;XRCC2
hsa04730	Long-term depression	2.71441441	0.03580044	0.76877909	CRHR1;GNAZ;IGF1R;JMJD7-PLA2G4B;PRKG1
hsa04270	Vascular smooth muscle contraction	2.06812527	0.03912026	0.76877909	CALD1;CALM2;JMJD7- PLA2G4B;MYH11;PLA2G10;PLA2G12A;PRKG1;RO CK1
hsa04010	MAPK signaling pathway	1.64178291	0.03951129	0.76877909	CACNA2D2;ELK4;FGFR1;IGF1R;INSR;JMJD7- PLA2G4B;JUN;KIT;MAP2K4;MAP2K5;MAP3K8;MA PK9;NF1;RASGRP4;TGFBR1
hsa00592	alpha-Linolenic acid metabolism	3.87773488	0.04021315	0.76877909	JMJD7-PLA2G4B;PLA2G10;PLA2G12A
hsa04114	Oocyte meiosis	2.1840116	0.04055251	0.76877909	CALM2;CDC27;CDK2;CPEB2;IGF1R;YWHAB;YWHA H
hsa04152	AMPK signaling pathway	2.15919328	0.04273663	0.76877909	CD36;IGF1R;INSR;PFKP;STRADB;TSC1;ULK1
hsa03018	RNA degradation	2.32664093	0.04324382	0.76877909	DHX36;EXOSC1;EXOSC9;PATL1;PFKP;XRN2
hsa05418	Fluid shear stress and atherosclerosis	1.8937775	0.04785156	0.7740514	CALM2;EDN1;GSTO2;GSTT1;JUN;MAP2K4;MAP2K 5;MAPK9;PTK2
hsa04072	Phospholipase D signaling pathway	1.87920998	0.04983654	0.7740514	INSR;JMJD7- PLA2G4B;KIT;LPAR5;LPAR6;PIK3R5;PIP5K1A;PTK2 B;TSC1

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Rank	Gene	Rank	Gene	Rank	Gene	Rank	Gene
1	DDR1	27	YES1	53	KLHL3	79	ZNF215
2	JUN	28	MAP2K4	54	BROX	80	GPIHBP1
3	IGF1R	29	EMILIN2	55	BRMS1L	81	DKK 2
4	ILK	30	PPHLN1	56	CDH24	82	FGFBP1
5	TGFBR1	31	PIKFYVE	57	MORN1	83	WFDC1
6	ACTR1A	32	ZNF12	58	CPNE8	84	TAF1L
7	PTK2	33	NAA38	59	NLRP2	85	ASPM
8	SLC39A14	34	ODF2	60	CDKN1C	86	LRRC15
9	HNRNPAB	35	PLCE1	61	MICU3	87	GZMM
10	PAPLN	36	PHKA1	62	GNAZ	88	DYNLRB2
11	FBRS	37	MAST3	63	CHEK2	89	CDCA2
12	RHOQ	38	PI4K2B	64	IPCEF1	90	CCR4
13	SH3GLB2	39	STRADB	65	NPR 3	91	ADGRG3
14	KDM5B	40	PSMG1	66	CENPN	92	EPHA6
15	RIOK3	41	ADGRD1	67	GALNT16	93	CCL23
16	RAVER1	42	TFAM	68	RNF168	94	DRICH1
17	BRWD1	43	LPCAT4	69	CHEK1	95	GRPR
18	VDAC3	44	EXOSC1	70	PRKAR2B	96	CCL7
19	SLC30A5	45	C190RF12	71	IL1RL1	97	CHRM4
20	ROCK1	46	IFT88	72	ESPN	98	OR2T33
21	MAPK9	47	ZNHIT6	73	ZNF311	99	NXF3
22	PSMC6	48	DSE	74	SPTB	100	LINC00303
23	MBD1	49	DNAJB14	75	PLK4	101	C5ORF52
24	ACSF2	50	ATAD2B	76	LHX6	102	CGA
25	PIP5K1A	51	TNK1	77	IL17RB	103	GHRHR
26	FXR2	52	MST1R	78	TAFA5	104	NPBWR1
						105	PRSS58

Gene Set	Description	ER	p-value	FDR	userID
hsa00562	Inositol phosphate metabolism	12.4504132	2.71E-04	0.08684954	PI4K2B;PIKFYVE;PIP5K1A;PLCE1
hsa04070	Phosphatidylinositol signaling system	8.17639077	0.00135647	0.14928134	PI4K2B;PIKFYVE;PIP5K1A;PLCE1
hsa04510	Focal adhesion	4.77748414	0.00142132	0.14928134	IGF1R;ILK;JUN;MAPK9;PTK2;ROCK1
hsa04012	ErbB signaling pathway	7.50435866	0.00186602	0.14928134	JUN;MAP2K4;MAPK9;PTK2
hsa05161	Hepatitis B	5.14866712	0.00264373	0.16012159	JUN;MAP2K4;MAPK9;TGFBR1;VDAC3
hsa04657	IL-17 signaling pathway	6.29676071	0.00354378	0.16012159	CCL7;IL17RB;JUN;MAPK9
hsa01522	Endocrine resistance	6.22520661	0.00369297	0.16012159	IGF1R;JUN;MAPK9;PTK2
hsa05142	Chagas disease (American trypanosomiasis)	6.01998002	0.00416611	0.16012159	JUN;MAP2K4;MAPK9;TGFBR1
hsa04933	AGE-RAGE signaling pathway in diabetic complications	5.89051808	0.00450342	0.16012159	JUN;MAPK9;PLCE1;TGFBR1
hsa05166	Human T-cell leukemia virus 1 infection	3.5883287	0.00593565	0.18994093	CHEK1;CHEK2;JUN;MAP2K4;TGFBR1;VDAC3
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Gene Set	Description	ER	p-value	FDR	userID
C0017636	Glioblastoma	4.18372924	2.60E-04	0.87999591	BRD2;CDK6;GSTT1;MDM4;MLH3;NF1;PROM1;PTK 2;SUZ12
C1866934	Decreased to absent deep tendon reflexes	4.44936284	0.00481712	1	ATM;CNTNAP1;ERCC5;PEX11B;RRM2B
C3278401	Hair hypopigmentation	7.78638498	0.00579311	1	ATM;LPAR6;LYST
C0005910	Body Weight	7.78638498	0.00579311	1	CDKAL1;GP2;MAP2K5
C0271650	Impaired glucose tolerance	5.19092332	0.00662433	1	ATM;CD36;INSR;ZMPSTE24
C2749675	Cortical gyral simplification	7.18743229	0.00735464	1	CDK6;FOXG1;PLK4
C0013405	Dyspnea, Paroxysmal	7.18743229	0.00735464	1	MYH11;PRKG1;TGFBR1
C0392775	Cystic medial necrosis of aorta	7.18743229	0.00735464	1	MYH11;PRKG1;TGFBR1
C1836635	Loeys-Dietz Aortic Aneurysm Syndrome	7.18743229	0.00735464	1	MYH11;PRKG1;TGFBR1
C1836653	Ascending aortic dissection	7.18743229	0.00735464	1	MYH11;PRKG1;TGFBR1

Supplementary Table s2. Pharmacologic screening, over-representation analysis, and gene expression of macropinocytosis screen hits. A, Compounds used in pharmacologic screening of ATC macropinocytosis. Abbreviations: Insulin-like growth factor 1 receptor(IGF1R); Insulin receptor(IR); pentose phosphate pathway(PPP); glucose-6-phosphate dehydrogenase(G6PG); AMP-activated protein kinase(AMPK). B, Top 20 enriched KEGG pathways using 543 mapped hit genes from the published gain-offunction macropinocytosis screen (ref. 40). C, Top 10 KEGG pathways using the top 102 mapped genes from the published gain-of-function macropinocytosis screen (ref. 40). D, Top 10 disease / gene associations from Disgenet, using 543 mapped hit genes from the published gain-of-function macropinocytosis screen (ref. 40). E, Gene expression of macropinocytosis screen hits in thyroid cancer TCGA data, ranked and corresponding to Figure 5A.