

**Supplementary Table S1. Primer sets used in this study**

Gene ID	Forward Primer Sequence Reverse Primer Sequence	Note
<i>For quantitative reverse-transcription real-time PCR (qRT-PCR)</i>		
GAPDH	5' -CAGCAAGAGCACAAGAGGAA-3' 5' -TCTACATGGCAACTGTGAGGAG-3'	Loading control
MYC	5' -ACGTCTCCACACATCAGCAC-3' 5' -CGCCTCTTGACATTCTCCTC-3'	
p21	5' -CATGTGGACCTGTCACTGTCTT-3' 5' -GGATTAGGGCTTCCTCTTGG-3'	
RUNX2	5' -TCTGACCGCCTCAGTGATTT-3' 5' -TGTAATCTGACTCTGTCCTTGTGG-3'	
<i>For Chromatin Immunoprecipitation (ChIP)</i>		
2q24	5' -GCAATCCTGAGCGGACATAC-3' 5' -CCTGCTGCACTCTTGACCT-3'	Loading Control 1: Genomic region with no copy number change
RUNX2 +1L	5' -TCACTACCAGCCACCGAGA-3' 5' -GGCTCACGTCGCTCATTT-3'	Transcription start site II (TSS II)
RUNX2 +1S	5' -CCTCCTTGCCCCTCATTT-3' 5' -GGCTCACGTCGCTCATTT-3'	Transcription start site I (TSS I)
RUNX2 -250L	5' -TACAGGAGTTTGGGCTCCTTC-3' 5' -CTTTTCCCCCTTGCTCTTTC-3'	250 bp upstream of TSS II
RUNX2 -250S	5' -CGACTTACCTCTTGGCACCTT-3' 5' -CTGCACGCTCAGATTCCTC-3'	250 bp upstream of TSS I
RUNX2 -5KL	5' -TTAAACCTTCAACAACCTCCTTT-3' 5' -TTCATGTTAATGGCTTGCTCT-3'	Loading Control II: 5000 bp upstream of TSS II
RUNX2 -5KS	5' -CTCTTGTTACAGCCATGCAAA-3' 5' -CCAACTGTGTTGCACATGATTAC-3'	Loading Control III: 5000 bp upstream of TSS I
RUNX2 H3KAc27-2	5' -TCAAGTGGACCAGGGTTTTG-3' 5' -CTCCGATGACCACTTTAGGA-3'	H3KAc27 histone acetylation site 2
RUNX2 H3KAc27-3	5' -GTGTCCCTCCTTTGCACTCT-3' 5' -GCATGTGGAAACTGTGCTCT-3'	H3KAc27 histone acetylation site 3

**Supplementary Table S2. Antibodies used in this study.**

<b>Antibody</b>	<b>Phosphorylation Site</b>	<b>Company</b>	<b>Catalog No</b>
<i>For Western blotting</i>			
GAPDH		Santa Cruz	sc-47724
c-MYC		Santa Cruz	sc-40
SIRT1		Santa Cruz	sc-15404
p21		Cell Signaling	2946
Phospho-S6K	Thr389	Cell Signaling	9205
PARP		Cell Signaling	9532
Phospho-c-JUN	Ser63	Santa Cruz	sc-822
c-FOS		Santa Cruz	sc-52
Phospho-JAK2	Tyr1007/1008	Cell Signaling	3776
Phospho-JAK3	Tyr980/981	Cell Signaling	5031
Phospho-STAT3	Tyr705	Cell Signaling	9131
Phospho-STAT5	Tyr694	Cell Signaling	9356
caspase-3		Cell Signaling	9668
caspase-7		Cell Signaling	9502
caspase-8		Cell Signaling	9746
caspase-9		Santa Cruz	sc-6138
<i>For Chromatin Immunoprecipitation (ChIP)</i>			
BRD4		Bethyl Lab	A301-985A50

**Supplementary Table S3. Concentration ratio of JQ1 and rapamycin used in the drug combination study.** ID numbers correspond to the point numbers in isobolograms in Figure 4C. ND = not done.

ID	MNNG/HOS		SJSA	
	JQ1 ( $\mu$ M)	rapamycin (nM)	JQ1 ( $\mu$ M)	rapamycin (nM)
1	0.78	1.51	1.51	3.13
2	0.78	3.13	1.51	6.25
3	0.78	6.25	1.51	12.50
4	0.78	12.50	1.51	25.00
5	1.51	1.51	1.51	50.00
6	1.51	3.13	3.13	3.13
7	1.51	6.25	3.13	6.25
8	1.51	12.50	3.13	12.50
9	3.13	1.51	3.13	25.00
10	3.13	3.13	3.13	50.00
11	3.13	6.25	6.25	3.13
12	3.13	12.50	6.25	6.25
13	6.25	1.51	6.25	12.50
14	6.25	3.13	6.25	25.00
15	6.25	6.25	6.25	50.00
16	6.25	12.50	12.50	3.13
17	12.50	1.51	12.50	6.25
18	12.50	3.13	12.50	12.50
19	12.50	6.25	12.50	25.00
20	12.50	12.50	12.50	50.00
21	25.00	1.51	25.00	3.13
22	25.00	3.13	25.00	6.25
23	25.00	6.25	25.00	12.50
24	25.00	12.50	25.00	25.00
25	ND	ND	25.00	50.00

**Supplementary Table S4. Significantly downregulated genes in JQ1-treated cells vs. control.**

MNNG/HOS cells were treated with JQ1 (7.5  $\mu$ M), rapamycin (12.5 nM), or both for 6 h and subjected to microarray analysis. Among differentially expressed genes (DEGs), those significantly downregulated in JQ1-treated cells are ranked according to the log<sub>2</sub> ratio of gene expression level in JQ1-treated cells compared to gene expression level in DMSO-treated control. Genes with ratio of -2 or lower are shown. The position of RUNX2 is highlighted in yellow.

RANK	SYMBOL	ENTREZ_GENE_ID	log2 JQ1/Ctrl
1	RIN2	54453	-4.092148585
2	IL7R	3575	-3.92117468
3	KCNF1	3754	-3.719257132
4	IL7R	3575	-3.70296854
5	ZMYND8	23613	-3.691144216
6	ZMYND8	23613	-3.58703991
7	WNT5A	7474	-3.550375313
8	C15orf52	388115	-3.538340925
9	KLHL14	57565	-3.466262418
10	TNFRSF11B	4982	-3.272617415
11	PSCDBP	9595	-3.226055228
12	PIGC	5279	-3.217367635
13	CH25H	9023	-3.047854426
14	DCLRE1A	9937	-3.035346585
15	CSF2	1437	-3.027063714
16	CHRNA9	55584	-2.990436969
17	ZNF586	54807	-2.969226857
18	GPR81	27198	-2.966484586
19	C21orf63	59271	-2.966446172
20	E2F2	1870	-2.897758158
21	LYPD1	116372	-2.890716213
22	SHROOM2	357	-2.867196133
23	NUAK1	9891	-2.849689676
24	WNT7B	7477	-2.84927751
25	KRT80	144501	-2.831350867
26	RASL10A	10633	-2.827005919
27	BCL3	602	-2.821717989
28	SOX21	11166	-2.815924038
29	CLCF1	23529	-2.815777088
30	TRIB2	28951	-2.796699998
31	ZNF827	152485	-2.784693885
32	OTUB2	78990	-2.777207795
33	ARL14	80117	-2.727708179
34	PHF15	23338	-2.688054101
35	CDCP1	64866	-2.679191408
36	ZNF586	54807	-2.664450479
37	LOC100216001	100216001	-2.640809887
38	C1orf106	55765	-2.622366147
39	PIGC	5279	-2.619634504
40	SLC16A6	9120	-2.604624355
41	FAM109B	150368	-2.602747683
42	CCDC102A	92922	-2.586393799

43 RASL12	51285	-2.583817136
44 TMEM156	80008	-2.582348799
45 STAMBPL1	57559	-2.520267239
46 HOXA2	3199	-2.518485708
47 MEIS2	4212	-2.507727949
48 ZNF365	22891	-2.494896233
49 NUAK1	9891	-2.492668761
50 MBP	4155	-2.47567176
51 LRRN3	54674	-2.459340453
52 C16orf30	79652	-2.451614536
53 TRIB3	57761	-2.441376083
54 ACOT4	122970	-2.438143334
55 MMACHC	25974	-2.436182863
56 SH3RF2	153769	-2.428049225
57 LOC100134073	100134073	-2.424971825
58 GPR68	8111	-2.420483805
59 SPRY1	10252	-2.413695733
60 TOMM40L	84134	-2.409498866
61 NME6	10201	-2.408962335
62 HAS2	3037	-2.403004982
63 GREM1	26585	-2.394335179
64 PRDM10	56980	-2.394076176
65 FAM176A	84141	-2.379910336
66 SPRY1	10252	-2.376294982
67 ARID2	196528	-2.374576522
<b>68 RUNX2</b>	<b>860</b>	<b>-2.370703936</b>
69 DKK1	22943	-2.367125021
70 HOXA2	3199	-2.348330668
71 SOX2	6657	-2.348291893
72 PTHLH	5744	-2.341577334
73 L3MBTL3	84456	-2.33117637
74 CHMP6	79643	-2.321825037
75 IRX4	50805	-2.321716365
76 TMEM166	84141	-2.313704023
77 KIAA1333	55632	-2.301177069
78 CCRK	23552	-2.294081999
79 IRS1	3667	-2.287137125
80 CDC42EP1	11135	-2.257127921
81 PLCL2	23228	-2.255246569
82 KIAA0753	9851	-2.244058663
83 ABCA1	19	-2.234814999
84 FAM174B	400451	-2.22553054
85 NME6	10201	-2.217212699
86 USP21	27005	-2.199877641
87 ZFP112	7771	-2.199332591
88 PLD6	201164	-2.197773804
89 C17orf100	388327	-2.184385786
90 HOXC9	3225	-2.182666652
91 PFAAP5	10443	-2.179490397
92 UQCR	10975	-2.171227943
93 BNIP1	662	-2.165496148
94 LRFN4	78999	-2.165296854

95 GPRC5C	55890	-2.160979937
96 C9orf64	84267	-2.151883313
97 ZNF689	115509	-2.147001719
98 SFMBT1	51460	-2.141236613
99 TMEM156	80008	-2.138354315
100 FOXA2	3170	-2.13571766
101 LOC730525	730525	-2.127931712
102 HOXA10	3206	-2.12126226
103 RG9MTD3	158234	-2.112530199
104 PTHLH	5744	-2.110597205
105 EDARADD	128178	-2.107474541
106 IL1RAPL1	11141	-2.094175708
107 FAM50B	26240	-2.090266317
108 ZNF323	64288	-2.087979724
109 HMGA2	8091	-2.087670102
110 RIPPLY2	134701	-2.085783283
111 HOXC8	3224	-2.080610309
112 ELFN2	114794	-2.06967568
113 VEGFC	7424	-2.068131701
114 TSPYL3	128854	-2.062710885
115 ARID2	196528	-2.062269137
116 C19orf12	83636	-2.056408866
117 RXRA	6256	-2.053874538
118 ZFHX3	463	-2.052255426
119 SCHIP1	29970	-2.050903463
120 ELF2	1998	-2.048195781
121 PHOSPHO2	493911	-2.046147291
122 ZNF573	126231	-2.045996162
123 IL28RA	163702	-2.042259309
124 NEK6	10783	-2.042104516
125 GMEB1	10691	-2.041652796
126 IRAK3	11213	-2.040076632
127 ZNF248	57209	-2.03729212
128 ZFP64	55734	-2.034323054
129 UNC50	25972	-2.031883093
130 KCTD14	65987	-2.021823568
131 NEXN	91624	-2.020985309
132 WDR4	10785	-2.019857938
133 FAM176A	84141	-2.019339471
134 TMEM204	79652	-2.019084788
135 THUMPD3	25917	-2.017595711

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**Supplementary Table S5. Significantly upregulated genes in JQ1-treated cells vs. control.** MNNG/HOS cells were treated with JQ1 (7.5  $\mu$ M), rapamycin (12.5 nM), or both for 6 h and subjected to microarray analysis. Among differentially expressed genes (DEGs), those significantly upregulated in JQ1-treated cells are ranked according to the log<sub>2</sub> ratio of gene expression level in JQ1-treated cells compared to gene expression level in DMSO-treated control. Genes with ratio of 2 or higher are shown. The position of p21 (CDKN1A) is highlighted in yellow.

RANK	SYMBOL	ENTREZ_GENE_ID	log2 JQ1/Ctrl
1	FGFR3	2261	3.973535301
2	LMO2	4005	3.696380122
3	FOS	2353	3.631029668
4	ARC	23237	3.537490533
5	HIST1H2BD	3017	3.342158837
6	TXNIP	10628	3.259420968
7	HES6	55502	3.101914333
8	CRISPLD2	83716	3.059225419
9	MARCH3	115123	2.983932173
10	SERPINI1	5274	2.982531459
11	METRNL	284207	2.933443418
12	HIST2H4A	8370	2.873400264
13	ZFP36	7538	2.83986895
14	HIST1H2BD	3017	2.83977155
15	PPP1R13B	23368	2.831797532
16	SERTAD1	29950	2.820421633
17	FAM46C	54855	2.806971275
18	CTGF	1490	2.795179074
19	GCH1	2643	2.736704706
20	HIST2H2BE	8349	2.696665348
21	HIST2H4B	554313	2.671971803
22	CDKN1A	1026	2.662644165
23	MERTK	10461	2.638666174
24	FZD9	8326	2.612581327
25	MARCH3	115123	2.602913932
26	C1orf124	83932	2.593468877
27	KIAA1683	80726	2.545875435
28	IRF7	3665	2.535118396
29	KCNK12	56660	2.497182187
30	GLS	2744	2.459447038
31	LOC648164	648164	2.456782629
32	METRNL	284207	2.446016489
33	TUFT1	7286	2.431334717
34	HIST1H2BG	8339	2.428113897
35	LOC100133609	100133609	2.412090776
36	PELI1	57162	2.405895428
37	CTGF	1490	2.399297795
38	BAIAP2	10458	2.386815135
39	DACT3	147906	2.372508049
40	RASD1	51655	2.372201292
41	CHCHD7	79145	2.352793862

42 HIST1H2AC	8334	2.341376436
43 HSPA2	3306	2.325390118
44 SLC30A3	7781	2.324112089
45 HIST1H3G	8355	2.311199287
46 HSPA2	3306	2.302839838
47 KBTBD9	114818	2.301358687
48 HIST1H3H	8357	2.279922294
49 ADARB1	104	2.268314194
50 NPTX2	4885	2.266003732
51 GCH1	2643	2.234991108
52 SLC6A8	6535	2.224829048
53 B3GNT2	10678	2.209458483
54 HIST1H3D	8351	2.186439887
55 LOC649679	649679	2.179136833
56 HIST1H2AG	8969	2.173989433
57 GRM2	2912	2.164843419
58 CSRNP2	81566	2.156020479
59 LOC100129907	100129907	2.147408872
60 PPP2R2B	5521	2.140786247
61 MAFB	9935	2.133603564
62 CASZ1	54897	2.128990836
63 METRNL	284207	2.126617893
64 HSPA12A	259217	2.100170803
65 WDR47	22911	2.09019125
66 MT1X	4501	2.084063745
67 TRIM36	55521	2.07962244
68 HSPA1A	3303	2.063880928
69 RRAD	6236	2.06021117
70 MGC61598	441478	2.05274149
71 PEG10	23089	2.050900521
72 IL11	3589	2.04726304
73 SLC6A10P	386757	2.046182421
74 TUBB4Q	56604	2.0348669
75 STARD5	80765	2.022056802
76 CORO1A	11151	2.021619824
77 MKNK2	2872	2.019313893
78 LOC653506	653506	2.019166814
79 AMACR	23600	2.015237947
80 PLEKHO2	80301	2.000865846

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**Supplementary Table S6. Significantly downregulated genes in JQ1 and rapamycin-treated cells vs. JQ1-treated cells.** MNNG/HOS cells were treated with JQ1 (7.5  $\mu$ M), rapamycin (12.5 nM), or both for 6 h and subjected to microarray analysis. Among differentially expressed genes (DEGs), those significantly downregulated in JQ1 and rapamycin-treated cells are ranked according to the log<sub>2</sub> ratio of gene expression level in JQ1 and rapamycin-treated cells compared to gene expression level in JQ-treated cells. Genes with ratio of -2 or lower are shown. Only one gene met the criteria.

<b>RANK</b>	<b>SYMBOL</b>	<b>ENTREZ_GENE_ID</b>	<b>log2 (JQ1+rapamycin)/JQ1</b>
1	LOC653375	653375	-2.143630169

**Supplementary Table S7. Significantly upregulated genes in JQ1 and rapamycin-treated cells vs. JQ1-treated cells.** MNNG/HOS cells were treated with JQ1 (7.5  $\mu$ M), rapamycin (12.5 nM), or both for 6 h and subjected to microarray analysis. Among differentially expressed genes (DEGs), those significantly upregulated in JQ1 and rapamycin-treated cells are ranked according to the log<sub>2</sub> ratio of gene expression level in JQ1 and rapamycin-treated cells compared to gene expression level in JQ-treated cells. Genes with ratio of 2 or higher are shown.

RANK	SYMBOL	ENTREZ_GENE_ID	log <sub>2</sub> (JQ1+rapamycin)/JQ1
1	DDIT3	1649	3.622533331
2	RCAN1	1827	2.992555073
3	FBXO32	114907	2.615711453
4	MT1H	4496	2.504426997
5	SCARNA23	677773	2.464839341
6	PIM1	5292	2.363368461
7	TRIB3	57761	2.357321024
8	HBP1	26959	2.331455212
9	ATF3	467	2.304204638
10	C5orf41	153222	2.243318829
11	KLHL24	54800	2.21134671
12	GEM	2669	2.199837007
13	MT1M	4499	2.177666136
14	MT1E	4493	2.164168459
15	GEM	2669	2.126787166
16	FBXO32	114907	2.125135898
17	SESN2	83667	2.094470304
18	MT1G	4495	2.09191185
19	MIR330	442902	2.070090675
20	INSIG1	3638	2.05617522
21	IL8	3576	2.045354136