Supplemental Information

Supplemental Figure Legends

Figure S1, Related to Figure 1. KRAS rescue screen using kinase library. KRAS complementation screen using kinase ORF library of ~600 kinases, including common oncogenic activating mutations. Screen was performed in the same manner as described for Figure 1. Genes scoring 3SD above negative controls are labeled.

Figure S2, Related to Figure 2. Interrogation of YAP1 and KRAS signaling. (A) Assessment of YAP1 ability to rescue cell proliferation after PI3K inhibition. Cells were plated at 50,000 cells per well in 12-well plates in triplicate and were treated with 1 uM GDC-0941 or DMSO for 48 hours. Cells were counted using Vi-Cell Cell Viability Analyzer (Beckman Coulter). Mean +/- SD shown, n=3. (B) Confirmation of shYAP1 gene suppression by immunoblot, corresponding to colony formation (See Fig. 2E). (C) Assessment of Hpo pathway or YAP1 phosphorylation by suppression or expression of KRAS. (D) Assessment of GTP-bound KRAS levels after YAP1 expression. (E). Immunoblot of AKT or ERK activation corresponding to inhibitor treatment in Fig. 2G. (C-E) Dox indicates presence (+) or absence (-) of doxycycline treatment, which induces shKRAS expression.

Figure S3, Related to Figure 3. Effect of YAP1 structural mutations on YAP1 function. (A) Effect of expressing TEAD2-VP16 on the activity of a TEAD-specific reporter in 293T cells. Data represent mean +/- SD, n=3. (B) Expression of TEAD2-VP16 in HCT116 corresponding to Fig. 3D. (C) YAP1$^{\Delta SH3bm}$ rescues suppression of KRAS in HCTtetK cells. (D) YAP1^{Y357F} rescues suppression of KRAS in HCTtetK cells. (C,D) Viability of doxycycline treated (KRAS suppressed) relative to untreated samples displayed. Mean +/- SD shown, n=3. (E) Immunoblot of YAP1 expression corresponding to Fig. 3B,C. *, protein not expressed. (F) Ability of YAP1

mutants to replace KRAS in transformation of HA1E as assessed by colony formation assay. Mean +/- SD shown, n=3.

Figure S4, Related to Figure 4. Identification and functional assessment of transcriptional motifs enriched in KRAS- and YAP1-regulated genes. (A) Gene expression in HCTtetK cells expressing indicated ORFs upon doxycycline treatment (shKRAS induction) for 48 h compared to media alone. Gene expression change in doxycycline compared to media is displayed in the heatmap. Red, relative decrease in expression upon doxycycline treatment; yellow, relative increase upon doxycycline treatment. Probes whose expression decreased (expression ratio <0.8 in doxycycline vs. untreated) upon KRAS suppression in negative controls (LacZ and $YAP^{\Delta TA}$) are displayed. Bar plot indicates number of probes whose expression was maintained by expression of the indicated ORF. (B) Transcription factor motifs enriched in promoters of genes regulated by both YAP and KRAS. “Annotation” lists the transcription factor category represented in Fig. 4B. (C) Effect of expressing shRNA targeting gene families ATF, CREB, EGR, and SP on YAP1-induced anchorage-independent colony formation. Data is only shown for shRNAs that suppress the target gene by at least 25% as measured by qRT-PCR. Red color indicates genes for which at least two shRNAs suppress colony formation at least 70% of control shRNA. (D) Effect of FOS suppression on HCT116 soft agar colony formation. (E) Effect of FOS suppression on colony formation of YAP1-transformed or KRAS-transformed HA1E cells. (C-E) Mean +/- SD shown, n=3.

Figure S5, Related to Figure 5. Assessment of EMT markers by qRT-PCR. (A) qRT-PCR for additional EMT markers not shown in Fig. 5B. Mean +/- SD relative to expression in LacZ control shown, n=3. (B) qRT-PCR for EMT markers upon KRAS and YAP1 expression in pancreatic cancer cell line SU86.86. Mean +/- SD relative to expression in LacZ control shown, n=3. (C) Immunoblot confirmation of MYC suppression and gene expression corresponding to

Fig. 5D. (D) Confirmation of Slug suppression by qRT-PCR referring to Figure 5E. Mean +/- SD relative to expression in shLuciferase control shown, n=3.

Figure S6, Related to Figure 6. Confirmation of antibody binding specificity for protein and DNA Co-immunoprecipitation. (A) Co-immunoprecipitation to assess interaction of YAP1 and JUN. Antibodies targeting YAP1 and V5 were used for immunoprecipitation in cell lysates from HCT116 expressing YAP1 and V5-tagged JUN. *, IgG chains. MW, molecular weight. (B) Confirmation of FOS binding sites identified by ENCODE data in promoter regions of *VIM* and *SLUG*. Chromatin immunoprecipitation was performed using antibody targeting FOS or control IgG. Binding was quantified by standard DNA curve, and bars represent mean of 3 replicates normalized to promoter region binding of IgG. (C) Assessment of YAP1 chromatin binding to target genes after suppression of YAP1 in HCT116 cells by shRNA. Equal amounts of lysate were used for ChIP and equal volume of DNA was loaded for each condition for quantification relative to a standard curve from input DNA. Values represent mean of 3 replicates normalized to IgG.

Figure S7, Related to Figure 7. Supporting data for *in vivo* KRAS resistance model. (A) Monitoring expression of shKras by GFP expression on Day 0 compared to Day 4 or Day 35 of doxcycline treatment. Two GFP exposure times are shown for Day 0. Day 0 tumors are weakly GFP positive from the MSCV-luciferase-IRES-GFP vector. Representative lung images are shown corresponding to Fig. 7B, 7C. (B) Quantification of EMT markers in KP-Kras cells D21 on Dox (Kras OFF) compared to no Dox (Kras ON). Shown are average Log2 fold change across 3 replicates from RNA-seq data. (C) Expression of EMT markers in tumor cells that escape Kras suppression *in vivo* (n=4). n.s., $p>0.05$; *, $p<0.05$; **, $p<0.01$. (D) *In vitro* rescue of Kras suppression in KP-KrasA cells by human YAP1 and mouse Yap1. Relative viability is shown after suppression of Kras (dox) compared to without Kras suppression (media). Mean +/- SD

shown, n=3. (E) *In vivo* rescue of Kras suppression in KP-KrasA cells in orthotopic transplant model. *, P-value = 0.003. **, P-value = 0.007. (F) Yap1 expression level in parental cell line (Pre-Transplant) expressing shYap1 compared to *in vivo* tumors that arise (Relapsed tumors). Bars indicate mean +/- SD. Points indicate YAP1 expression in individual relapsed micro-dissected tumors corresponding to day 28 from experiment in Fig. 7G.

Supplemental Tables

Table S1, Related to Figure 1. Results of genome-scale KRAS complementation screen. Identities of screened ORFs are provided along with its infection rate (column "infection_rate), calculated as the ratio of viability between blasticidin-treated and untreated wells, and its average rescue score after normalization to negative controls ("adjusted_score").

Table S2, Related to Figure 1. In-cell western data for ERK and S6 activation. After expression of each gene, the average ratio of phospho-ERK intensity versus total-ERK intensity is annotated in column "ratio_dox_ERK." The average ratio of phospho-S6 intensity versus total-S6 intensity is annotated in column "ratio_dox_S6." Genes that activate ERK or S6 above 2 standard deviations from mean of negative controls are annotated with 'Y' in columns "ERK.2SD" and "S6.2SD," respectively.

Table S3, Related to Figure 4. Gene expression profiling in the context of KRAS suppression. HCTtetK cells expressing LacZ, YAP1, or KRAS were cultured for 30 hours in the presence of doxycycline (shKRAS expressed) or cultured without doxycycline. Relative ratio of gene expression in the doxycycline treated compared to untreated samples are provided. Genes suppressed upon doxycycline treatment (LacZ ratio <0.8) that are rescued by YAP1 (YAP1 ratio >0.8) or KRAS (KRAS ratio >0.8) are indicated by "yes" (Y) in the columns titled "Rescue.by.YAP?" and "Rescue.by.KRAS?," respectively.

Table S4, Related to Figure 6. Pathway analysis of YAP and FOS shared DNA binding targets. We performed Ingenuity Pathway Analysis to test for enrichment of gene sets amongst genes whose proximal promoters (1 kb upstream, 0.3kb downstream of transcription start site) were bound by both FOS and YAP1 using published ChIP-on-Chip data (See supplemental

methods). Gene sets enriched to p<0.05 are shown in the table. Control analysis of pathways enriched amongst genes bound by both FOS and AR is also provided for reference.

Table S5, Related to Figure 7. RNA data from KP-KrasA resistant cell profiling. This file includes tables for expression levels (in FPKM, Fragments Per Kilobase of transcript per Million mapped reads) per gene, and differential analysis between D0 and D21 time-points using the mouse RNA-seq dataset.

Table S6. shRNA sequences, Related to Experimental Procedures

shRNA	Source	Species	Target sequence
shKRAS	Broad (TRCN_010369)	human	CAGTTGAGACCTTCTAATTGG
shYAP1-1	Broad (TRCN_107266)	human	GCCACCAAGCTAGATAAAGAA
shYAP1-2	Broad (TRCN_107265)	human	CCCAGTTAAATGTTCACCAAT
shMYC-1	Broad (TRCN_039639)	human	CCCAAGGTAGTTATCCTTAAA
shMYC-2	Broad (TRCN_039640)	human	AATGTCAAGAGGCGAACACA

shFOS-1	Broad (TRCN_016004)	human	GCGGAGACAGACCAACTAGAA
shFOS-2	Broad (TRCN_273940)	human	TCTCCAGTGCCAACTTCATTC
shSLUG-1	Broad (TRCN_15389)	human	CCCATTCTGATGTAAAGAAAT
shSLUG-2	Broad (TRCN_15388)	human	GCCAAATCATTTCAACTGAAA
shLucif	Broad (TRCN_072261)	control	CACTCGGATATTTGATATGTG
shYap1-2		mouse	TGCTGTTGACAGTGAGCGCAAGATACTT CTTAAATCACAATAGTGAAGCCACAGAT GTATTGTGATTTAAGAAGTATCTTTTGCC TACTGCCTCGGA
shYap1-1		mouse	TGCTGTTGACAGTGAGCGAATGAATTAA CTCTGTGTATAATAGTGAAGCCACAGAT GTATTATACACAGAGTTAATTCATGTGC CTACTGCCTCGGA
shKras		mouse	TGCTGTTGACAGTGAGCGACAGACCCA GTATGAAATAGTATAGTGAAGCCACAGA TGTATACTATTTCATACTGGGTCTGCTG CCTACTGCCTCGGA

shRenilla		control	TGCTGTTGACAGTGAGCGCAGGAATTAT AATGCTTATCTATAGTGAAGCCACAGAT GTATAGATAAGCATTATAATTCCTATGCC TACTGCCTCGGA

Table S7. Primer sequences, Related to Experimental Procedures

Gene	Target	Species	Sequence
SNAI2 (Slug)	Promoter DNA	Human	5'-TGGGGCATGTCATTACACAG 3'-GGCTTGCGTTTTTACCACAT
SNAI2 (Slug)	3' Control DNA	Human	5'-CCCCTTGCCAGATGTTTCTA 3'-TGGCTGATAGCTTGACTGGA
VIM	Promoter DNA	Human	5'-GGCCCAGCTGTAAGTTGGTA 3'-CCTAGCGGTTTAGGGGAAAC
VIM	3' Control DNA	Human	5'-TTCACTGCAGCCAACAACTC 3'-GCCAGGTGTGTGGCTAGTTT
VIM	mRNA	Human	5'-GTGGACCAGCTAACCAACGACAAA-3 3'-TTCAAGGTCAAGACGTGCCAGAGA-3

FN1	mRNA	Human	5’-CGGTGGCTGTCAGTCAAAG 3’-AAACCTCGGCTTCCTCCATAA
SNAI2 (Slug)	mRNA	Human	5’-ACCTTGTGTTTGCAAGATCTGCGG-3 3’-TGCAAATGCTCTGTTGCAGTGAGG-3
ZEB1	mRNA	Human	5’-GATGATGAATGCGAGTCAGATGC 3’-ACAGCAGTGTCTTGTTGTTGT
CDH1	mRNA	Human	5’-CTGGGACTCCACCTACAGAAAGTT-3 3’-GAGGAGTTGGGAAATGTGAGCA-3
OCLN	mRNA	Human	5’-ACAAGCGGTTTTATCCAGAGTC 3’-GTCATCCACAGGCGAAGTTAAT
FOS	mRNA	Human	5’-CCGGGG ATAGCCTCTCTTACT 3’-CCAGGTCCGTGCAGAAGTC
SNAI1	mRNA	Human	5’-TCGGAAGCCTAACTACAGCGA 3’-AGATGAGCATTGGCAGCGAG
SOX10	mRNA	Human	5’-CCTCACAGATCGCCTACACC 3’-CATATAGGAGAAGGCCGAGTAGA
CDH2	mRNA	Human	5’-TCAGGCGTCTGTAGAGGCTT 3’-ATGCACATCCTTCGATAAGACTG

ZEB2	mRNA	Human	5’-CAAGAGGCGCAAACAAGCC 3’-GGTTGGCAATACCGTCATCC
TWIST1	mRNA	Human	5’-CTGCCCTCGGACAAGCTGAG 3’-CTAGTGGGACGCGGACATGG
Yap1	mRNA	Mouse	5’-ATGACAACCAATAGTTCCGATCC 3’-CAGGGTGCTTTGGCTGAT
Actb	mRNA	Mouse	5’-CTTTGCAGCTCCTTCGTTG 3’-GATGGAGGGGAATACAGCCC

Supplemental Experimental Procedures

Generation of HCTtetK cells

HCT116 cells were infected with lentivirus to integrate a doxycycline inducible KRAS shRNA (See Table S5) using the pLKO-Tet-On backbone (Novartis). Selection for cells harboring stable integration was achieved using 2 ug/mL of puromycin. Cells were seeded at 0.3 cells per well in 96-well plates to allow selection of clones. We assessed thirty clones and selected HCTtetK based on effectiveness of KRAS suppression upon doxycycline treatment.

In-Cell Western

Cells were seeded at 1000 cells per well in black with clear-bottom 384-well plates in 30 ul media. The following day, 30 ul media supplemented with 16ug/mL Polybrene was added to each well for infection with 1.5 ul virus containing each ORF. Each ORF was infected in duplicate wells. One day post-infection, 45 ul media was removed and replenished with 25 ul fresh media. Two days post-infection, an additional 30 ul media supplemented with 500 ug/mL doxycycline was changed each well. After doxycycline treatment for 30 hrs, cells were fixed using 25 ul 4% formaldehyde and 0.1% TX-100 in PBS for 30 min at RT. Fixative was washed off using 50 ul PBS. Blocking was performed using 25 ul Odyssey Blocking Buffer (LI-COR) for overnight at 4°C. 18 ul of primary antibody mix (1:500 dilution of anti-phospho-S6 (Cell Signaling #2211)+ 1:1000 dilution of anti-S6 (Cell Signaling #2317); or 1:500 dilution of anti-phospho-ERK (Cell Signaling #9101)+ 1:1000 dilution of anti-ERK (Santa Cruz sc-135900) in 0.1% Tween-20 in Odyssey Blocking Buffer) was incubated for 1 hr at RT. Washes were performed 3 times, 10 minutes each using 0.1% Tween-20 in PBS. 18 ul of secondary antibody mix (1:800 IRDye 680RD goat anti-mouse (LI-COR) +1:800 IRDye 800CW goat anti-rabbit (LI-COR) in 0.1% Tween-20 in Odyssey Blocking Buffer) was incubated for 1 hr at RT. Washes were again performed. A final rinse was performed using 50 ul PBS. Scanning was performed using LI-

COR Odyssey (680RD at intensity 7.0, 800CW at intensity 9.0) and quantification was performed using LICOR Image Studio software. Results are provided in Table S2.

Chromatin Immunoprecipitation

Cultured cells were fixed for 15 min at room temperature with 1% formaldehyde in PBS. Crosslinking was stopped using 2.5 M glycine. Cells were collected in RIPA buffer (Sigma) containing protease inhibitors (Roche). Sonication was performed for 23minutes at 40% intensity and samples were centrifuged to remove insoluble materials. 1 mg lysate was incubated with 10 ug of either YAP1 (Santa Cruz) or FOS (Santa Cruz) antibody overnight at 4°C. The next day 50 µl Protein G Sepharose (Sigma) was added for 2 hr at 4°C. The beads were then washed twice with cold RIPA followed by 5 washes with wash buffer (100 mM Tris-HCl pH = 8.5, 500 mM LiCl, 1% NP-40 (v/v), 1% deoxycholic acid (v/v), and another two washes with RIPA. Beads were resuspended in 100 µl of TE buffer, and DNA was reverse cross-linked by adding 200 µl of Talianidis buffer [70 mM Tris-HCl pH = 8, 1 mM EDTA, 1.5% SDS (w/v)] and incubating overnight at 65°C. Supernatant containing DNA was collected. DNA yield was quantified by Qubit fluorometer (Invitrogen). Equal amount of DNA (approx. 0.1ng) of each sample was used for qPCR. Primers were designed using UCSC Genome Browser (http://genome.ucsc.edu) for reported FOS binding sites upstream of VIM and SNAI2, and a genomic locus downstream of each gene was used as control. Detailed sequences are provided in Table S6.

Protein Co-immunoprecipitation Assay

Nuclear Complex Co-IP kit (Thermo Fisher) was used for co-immunoprecipitation. 200ug lysate was used per IP reaction. Immunoprecipitation was performed using 10ul YAP1 antibody (Cell Signaling #4912), 50ul V5-tagged magnetic beads (Fisher Scientific #5050600), or the corresponding amount of control antibodies (anti-GFP, Cell Signaling #2555; Dynabeads protein

G, Life Technologies #10004D). Anti-V5 antibody directly conjugated to HRP (Life Technologies #R96125) was used in cases where cross-reactivity to immunoglobulin heavy chains needed to be avoided.

Collection of RNA

RNA from cell lines were extracted using PerfectPure RNA Cell Kit (Fisher Scientific #2302820). RNA from mouse tumor tissue was extracted using TRIzol (Invitrogen) after tissue homogenization.

Reporter Assay

293T were transfected using TransIT-LT1 reagent (Mirus). 1 ug of each ORF was transfected together with 0.5 ug reporter (or control reporter) and 0.5 ug pLX-GFP construct. 24 hours post-transfection, cells were seeded in 30 ul media in 384-well plates. Reporter activity was assessed using Steady-Glo Luciferase Assay System (Promega), and normalized to total GFP fluorescence. TEAD reporter (8xGT-IIC-LucII) and control (delta-51-LucII) were obtained from RIKEN Bioresource Bank (http://dna.brc.riken.jp/), and AP1 reporter (pAP1(PMA)-TA-Luc) and control (pTA-Luc) were purchased from Clontech.

Microarray Processing

HCTtetK cells expressing LacZ, KRAS, or YAP1 were treated with doxycycline for 30 hours to suppress KRAS. Untreated cells expressing each ORF were used as control. RNA was collected using PerfectPure RNA Cultured Cell Kit (5Prime) and expression profiling was performed on Human Genome U133A 2.0 Array (Affymetrix) using the Dana Farber Cancer Institute Microarray Core. Signal intensities were estimated by Microarray Suite version 5.0 (MAS 5.0) using Affymetrix default analysis settings. Relative fold change in intensity between treated and untreated samples were calculated and are displayed in Table S3. Repeat

microarray data including YAP1^{S94A} and YAP1$^{\Delta TA}$ mutants were performed in a separate experiment according to procedures above. Data for both sets of data can be found in their entirety at NCBI Gene Expression Omnibus (GEO) database, Accession Number GSE55942.

Gene Expression Analysis

To identify enriched gene sets, we used genes co-regulated by both KRAS and YAP1 (Table S3) to query the MSigDB gene set database C2 collection of chemical and genetic perturbations (CGP) version accessed July 2011 (http://www.broadinstitute.org/gsea/msigdb). Statistical enrichment was measured by hypergenometric test per MSigDB website. To identify enriched transcription factors, we input the same gene list to query into the TransFind algorithm (Kielbasa, Klein, Roider, Vingron, & Bluthgen, 2010). As a list of "unregulated" gene sets, we input the list of genes regulated by KRAS alone but not by YAP1. Promoter regions of 1000 nucleotides were considered for each gene using TRANSFAC highest information database version 2009.4.

RNA-Seq Processing

Paired-end Illumina mRNA sequencing for nine samples yielded 51mer reads in the range of 38.5M to 88.6M pairs per sample. Reads were trimmed to remove traces of adapter sequence using the FASTX-Toolkit from the Hannon Laboratory (CSHL, http://hannonlab.cshl.edu/fastx_toolkit). Adapter-stripped reads were aligned with Tophat (ver. 2.0.5) (Trapnell, Pachter, & Salzberg, 2009) using mouse (mm9) transcriptome and genome annotation from the UCSC genome browser (Kent et al., 2002). Approximately 86%-94% of reads were aligned across samples. Transcript assembly, abundance estimation, and differential expression analysis were performed using Cufflinks (ver. 2.0.2)(Trapnell et al., 2010). Three replicates for each time-point (day 0, day 21), corresponding to each of three clones (KP-KrasA, KP-KrasB, and KP-KrasC), were grouped to derive significance of differential

expression across experimental conditions. Data can be found in the NCBI Gene Expression Omnibus (GEO) database, Accession Number GSE56175.

KRAS Activity Assay

Each assay was performed using 1 mg lysate using Ras Activation Assay Kit (Millipore).

Quantitative PCR

Primer sequences used for qRT-PCR and chromatin immunoprecipitation are detailed in Table S6.

Cell Culture

All cancer cell lines were cultured in RPMI-1640 (Invitrogen) supplemented with 10% FBS (Sigma) and 1% streptomycin and penicillin. HA1E immortalized cell line was cultured in alpha-MEM (Invitrogen) supplemented with 10% FBS. Mouse cell lines and 293T cells were cultured in DMEM (Invitrogen) supplemented with 10% FBS.

Lentiviral Infection

shRNA in pLKO.1 backbone was obtained directly from the RNAi Consortium (Root, Hacohen, Hahn, Lander, & Sabatini, 2006). Detailed shRNA identities are listed in Table S5. ORFs were cloned into plx-304 and do not express C-terminal V5 tag unless otherwise noted. Lentiviruses were produced in 293T cells using the three-vector system as described (Moffat et al., 2006). Cells were infected in media containing 8ug/ml polybrene and 1:20 dilution of virus for shRNA or 1:5 dilution of virus for ORFs. Infected cells were selected with 2 ug/ml puromycin for 2 days or 10 ug/ml blasticidin for 5 days depending on the selection marker.

Inhibitor Treatment

HCTtetK cells expressing LACZ or YAP1 were plated in 96-well plates on day 0. On day 1, media supplemented with doxycycline or media alone was added. On day 3, 1 uM GDC-0941, 1 uM AZD-6244, both inhibitors, or DMSO was added. On day 6, viability was quantified using CellTiterGlo.

Immunoblotting

Immunoblotting was performed using 40 ug cell lysate per sample on 4-12% Bis-Tris gels (Invitrogen NuPAGE) and transferred to nitrocellulose membrane. Primary antibodies were obtained from Santa Cruz (KRAS sc-30, ß-actin sc-1615, FOS H-125, MYC sc-764, ERK1/2 sc-135900) and Cell Signaling (PI3Kinase 110alpha #4255, p44/42 MAPK #9107, Phospho-S6 Ribosomal Protein #2211, S6 Ribosomal Protein #2317). Immunoblots were visualized by infrared imaging (LI-COR) with the exception of KRAS and MYC, visualized by chemiluminescence.

Analysis of Published ChIP-on-Chip and ChIP-Seq Data

A list of Yap-occupied genes in MCF10A cells ($p <= 0.05$) was obtained from (Zhao et al., 2008). Fos-occupied proximal promoters (1kb upstream and 0.3kb downstream of TSS, similar to Zhao et al. (2008)) in MCF10A-Er-Src cells were derived from peak calls generated by the ENCODE Analysis Working Group (ENCODE Project Consortium et al., 2012)(AWG, March 2012 Freeze) downloaded from the UCSC genome browser database (Kent et al., 2002). In the absence of a negative control for Fos binding in MCF10A cells, we chose to use a known positive control, AR [4] (Androgen Receptor), with the goal of testing for specificity of enrichment of Epithelial to Mesenchymal (EMT) pathway genes in the Yap-Fos target overlap set. The list of AR-occupied genes was obtained from Zhao et al. (2008). We used IPA (Ingenuity Systems, www.ingenuity.com) to test for enrichment of canonical pathways in the Yap-Fos and AR-Fos target overlap sets.

Supplemental References

ENCODE Project Consortium, Dunham, I., Kundaje, A., Aldred, S. F., Collins, P. J., Davis, C. A., Doyle, F., Epstein, C. B., Frietze, S., Harrow, J., et al. (2012). An integrated encyclopedia of DNA elements in the human genome. Nature *489*, 57–74.

Kent, W. J., Sugnet, C. W., Furey, T. S., Roskin, K. M., Pringle, T. H., Zahler, A. M., and Haussler, A. D. (2002). The Human Genome Browser at UCSC. Genome Res. *12*, 996–1006.

Kielbasa, S. M., Klein, H., Roider, H. G., Vingron, M., and Bluthgen, N. (2010). TransFind--predicting transcriptional regulators for gene sets. Nucleic Acids Research *38*, W275–W280.

Moffat, J., Grueneberg, D. A., Yang, X., Kim, S. Y., Kloepfer, A. M., Foo, S. Y., Stewart, S. A., Stockwell, B. R., Hacohen, N., Hahn, W. C., et al. (2006). A Lentiviral RNAi Library for Human and Mouse Genes Applied to an Arrayed Viral High-Content Screen. Cell *124*, 1283–1298.

Root, D. E., Hacohen, N., Hahn, W. C., Lander, E. S., and Sabatini, D. M. (2006). Genome-scale loss-of-function screening with a lentiviral RNAi library. Nat. Methods *3*, 715–719.

Trapnell, C., Pachter, L., and Salzberg, S. L. (2009). TopHat: discovering splice junctions with RNA-Seq. Bioinformatics *25*, 1105–1111.

Trapnell, C., Williams, B. A., Pertea, G., Mortazavi, A., Kwan, G., van Baren, M. J., Salzberg, S. L., Wold, B. J., and Pachter, L. (2010). Transcript assembly and quantification by RNA-Seq reveals unannotated transcripts and isoform switching during cell differentiation. Nat. Biotechnol. *28*, 511–515.

Zhao, B., Ye, X., Yu, J., Li, L., Li, W., Li, S., Yu, J., Lin, J. D., Wang, C.-Y., Chinnaiyan, A. M., et al. (2008). TEAD mediates YAP-dependent gene induction and growth control. Genes Dev. *22*, 1962–1971.