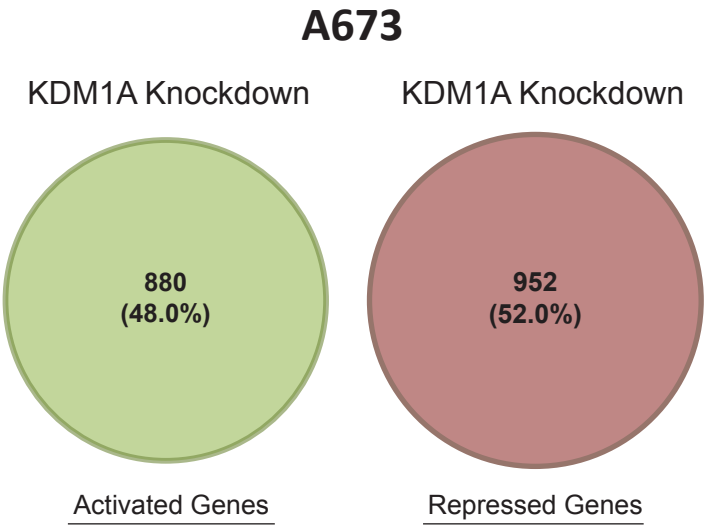
A



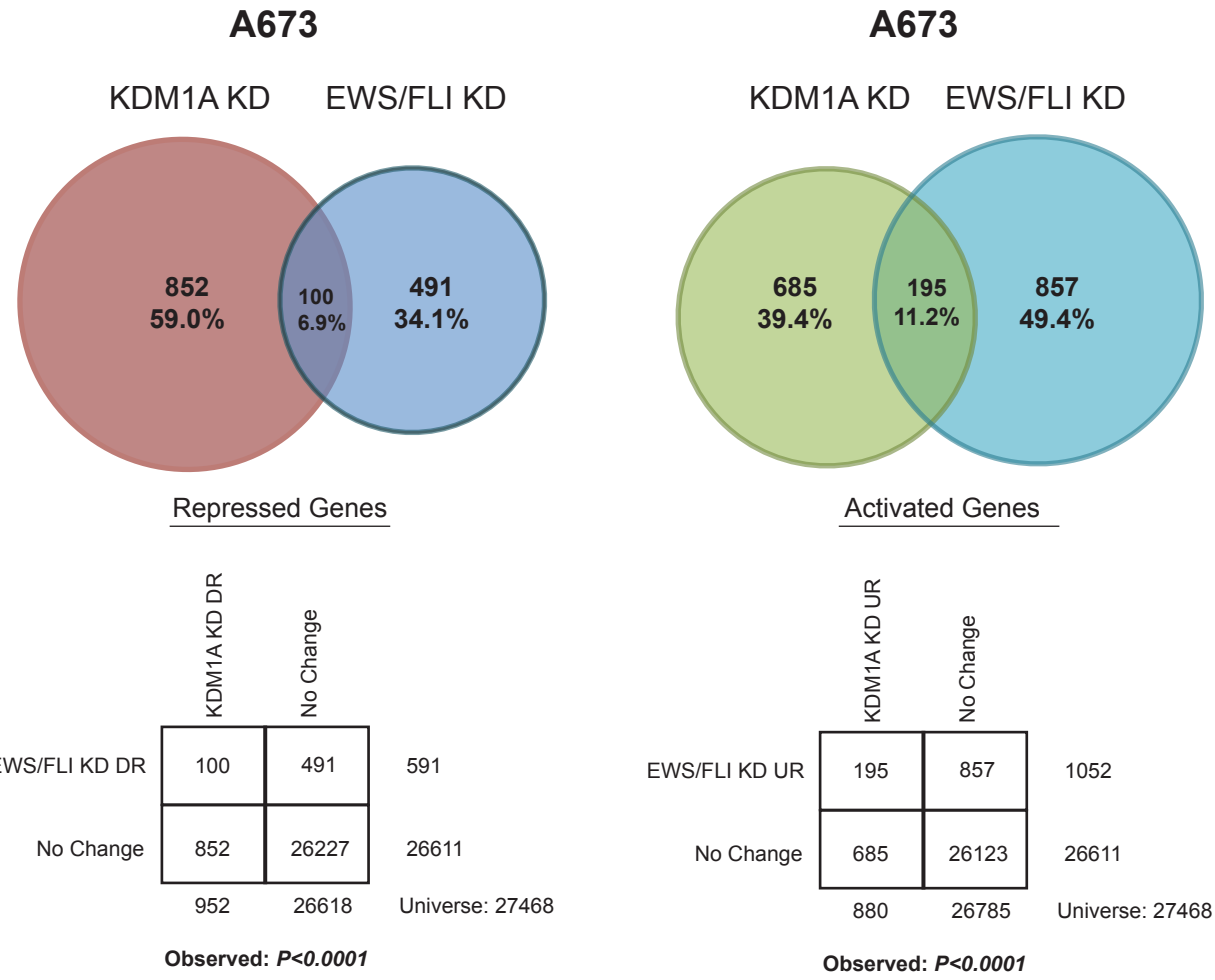
KDM1A Repressed Genes: *Activated* genes upon *KDM1A Knockdown*, (n=880)

Rank	Canonical Pathway	P-Value	Pathway Overlap	Genes
1	Hepatic Fibrosis/Hepatic Stellate Cell Activation	$7.51x10^{-09}$	25/181 (13.8%)	A2M, CCL2, CCR7, COL24A1, COL5A3, COL6A5, CTGF, CXCL8, EDN1, ICAM1, IL6, IL1A, IL1B, IL1R1, IL6R, KDR, LAMA1, LY96 MMP1, NFKB1, NGFR, PDGFA, PDGFB, SERPINE1, TNF
2	Granulocyte Adhesion and Diapedesis,	$2.50x10^{-08}$	23/165 (13.9%)	CCL2, CCL20, CCL26, CLDN12, CX3CL1, CXCL1, CXCL2, CXCL8. HRH1, ICAM1, ICAM2, IL1A, IL1B, IL1R1, ITGA3, ITGAM, MMP1, MMP3, MMP7, MMP12, NGFR, SELE, TNF
3	Agranulocyte Adhesion and Diapedesis	$7.62x10^{-08}$	23/175 (13.1%)	ACTG2, AOC3, CCL2, CCL20, CCL26, CLDN12, CX3CL1, CXCL1, CXCL2, CXCL8, HRH1, ICAM1, ICAM2, ILI1, IL1B, IL1R1, ITAG3, MMP1, MMP3, MMP7, MMP12, SELE, TNF
4	HMGB1 Signaling	$2.17x10^{-07}$	19/131 (14.5%)	CCL2, CNTF, CXCL8, ICAM1, IL6, IL11, IL1A, IL1B, IL1R1, LIF, MAP2K3, NFKB1, NGFR, PLAT, RHOJ, RND3, SELE, SERPINE1, TNF
5	TREM1 Signaling	$1.03x10^{-06}$	13/70 (18.6%)	CCL2, CXCL8, ICAM1, IL6, IL1B, ITGAX, NFKB1, STAT3, STAT5A, TLR1, TLR6, TLR7, TNF

KDM1A Activated Genes: *Repressed* genes upon *KDM1A Knockdown*, (n=952)

Rank	Canonical Pathway	P-Value	Pathway Overlap	Genes
1	Ethanol Degradation IV	$1.89x10^{-09}$	10/21 (47.6%)	ACSS1, ACSS2, ALDH2, ALDH2, ALDH1A1, ALDH1A3, ALDH1L1, ALDH1L2, ALDH7A1, CYGB, GPX7
2	Granzyme A Signaling	$9.04x10^{-08}$	8/17 (47.1%)	H1F0, HIST1H1A, HIST1H1B, HIST1H1C, HIST1H1D, HIST1H1E, HIST1H1T, HMGB2
3	Oxidative Ethanol	$9.04x10^{-08}$	8/17 (47.1%)	ACSS1, ACSS2, ALDH2, ALDH1A1, ALDH1A3, ALDH1L1, ALDH1L2, ALDH7A1,
4	Dopamine Degradation	$9.72x10^{-07}$	9/29 (31.0%)	ALDH2, ALDH1A1, ALDH1A3, ALDH1L1, ALDH1L2, ALDH7A1, SULT1A1, SULT1B1, SULT1E1
5	Histamine Degradation	$1.26x10^{-05}$	6/15 (40.0%)	ALDH2, ALDH1A1, ALDH1A3, ALDH1L1, ALDH1L2, ALDH7A1

B



C

KDM1A knockdown and EWS/FLI knockdown common repressed genes: *Activated upon knockdown (n=195)*

Rank	Canonical Pathway	p-Value	Pathway Overlap	Genes
1	Hepatic Fibrosis/Hepatic Stellate Cell Activation	$3.56x10^{-11}$	16/181 (8.8%)	A2M, CCL2, COL5A3, CTGF, CXCL8, EDN1, ICAM1, IL1A, IL1B, IL1R1, IL6R, KDR,LAMA1, PDGFA, PDGFB, SERPINE1
2	HMGB1 Signaling	$7.69x10^{-08}$	11/131 (8.4%)	CCL2, CXCL8, ICAM1, IL11,IL1B, ILIR1, LIF, PLAT, RND3, SERPINE1
3	Atherosclerosis Signaling	$4.08x10^{-06}$	9/124 (7.3%)	CCL2, COL5A3, CXCL8, ICAM1, IL1A, IL1B, PDGFA, PDGFB, PLA2G4C
4	Acute Phase Response Signaling	$7.02x10^{-06}$	10/168 (6.0%)	A2M, C1S, HMOX1, IL1A, IL1B, IL1R1, IL6R, SERPIND1, SERPINE1, SOCS3
5	Coagulation System	$2.32x10^{-05}$	5/35 (14.3%)	A2M, PLAT, PLAU, SERPIND1, SERPINE1

KDM1A knockdown and EWS/FLI knockdown common activated genes: *Repressed upon knockdown (n=100)*

Rank	Canonical Pathway	P-Value	Pathway Overlap	Genes
1	Complement System	$7.83x10^{-04}$	3/36 (8.3%)	C6, C7, ITGB2
2	The Visual Cycle	$4.06x10^{-03}$	2/19 (10.5%)	DHRS3, RBP1
3	Dopamine Degradation	$9.32x10^{-03}$	2/29 (6.9%)	SULT1A1, SULT1E1

D

E

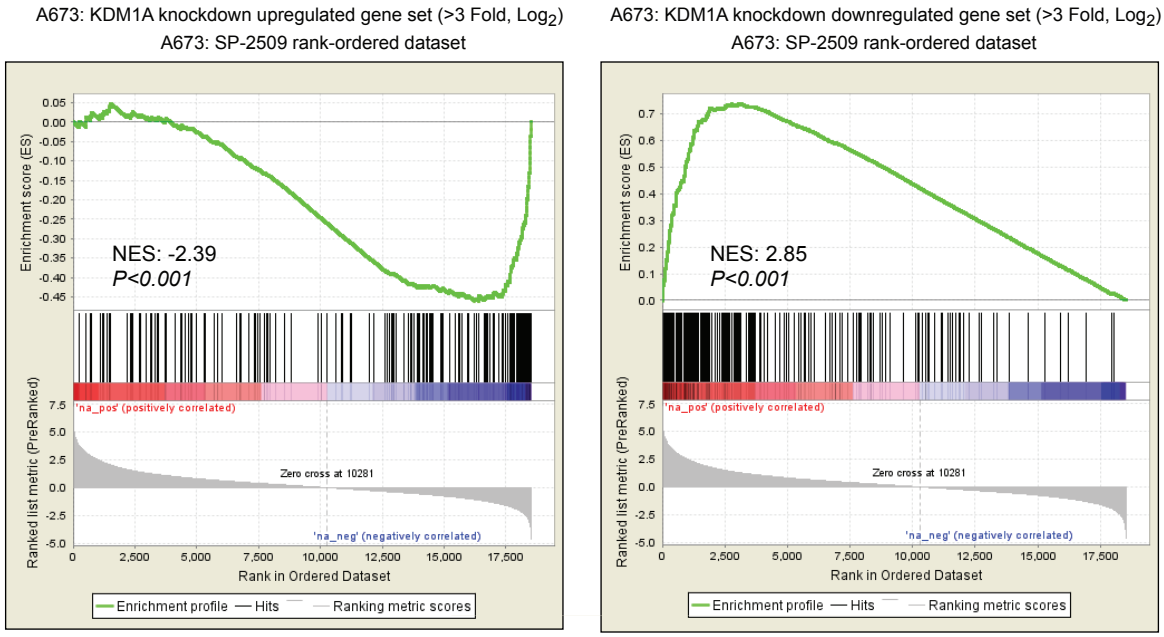
SP-2509 and KDM1A Knockdown (KD) common repressed genes: Activated upon KD/drug treatment (n=162)

Rank	Canonical Pathway	P-Value	Pathway Overlap	Genes
1	Granulocyte Adhesion and Diapedesis,	$1.29x10^{-06}$	10/165 (6.1%)	CCL26, CXCL1, CXCL2, CXCL8, ICAM1, IL1A, IL1R1, ITGA3, ITGAM, MMP3
2	Agranulocyte Adhesion and Diapedesis	$2.20x10^{-06}$	10/175 (5.7%)	AOC3, CCL26, CXCL1, CXCL2, CXCL8, ICAM1, IL1A, IL1R1, ITGA3, MMP3
3	HMGB1 Signaling	$1.45x10^{-05}$	8/131 (6.1%)	CXCL8, ICAM1, IL11, IL1R1, LIF, RND3, SERPINE1
4	Hepatic Fibrosis/Hepatic Stellate Cell Activation	$1.44x10^{-04}$	8/181 (4.4%)	CTGF, CXCL8, ICAM1, IL1A, IL1R1, IL6R, PDGFA, SERPINE1
5	IL-8 Signaling	$1.44x10^{-04}$	8/196 (4.1%)	CXCL1, CXCL8, HBEGF, HMOX1, ICAM1, ITGAM, ITGAX, RND3

SP-2509 and KDM1A Knockdown (KD) common activated genes: Repressed upon KD/drug treatment (n=107)

Rank	Canonical Pathway	P-Value	Pathway Overlap	Genes
1	Cell cycle: G2/M DNA Damage Checkpoint Regulation	$1.26x10^{-04}$	4/49 (8.2%)	AURKA, CDC25C, SKP2, TOP2A
2	Glycine Degradation (Creatine Biosynthesis)	$1.05x10^{-02}$	1/2 (50%)	GAMT
3	Thiosulfate Disproportionation III (Rhodanese)	$1.56x10^{-02}$	1/3 (33.3%)	TST

F



Supplementary Figure S2: *Targeted KDM1A inhibition and EWS/FLI knockdown induces similar transcriptional signatures*

(A) IPA of canonical pathways for genes commonly repressed and activated following KDM1A knockdown in A673 cells (>2 Log_2 fold change from iLuc scramble control). Venn diagram representations of the overlap between transcriptional profiles of **(B)** EWS/FLI and KDM1A knockdown or **(D)** KDM1A knockdown and SP-2509 treatment in A673 cells, generated through RNA-seq. Chi-square determined *P*-values are indicated with the observed contingency tables shown. IPA analysis of canonical pathways for genes commonly repressed and activated following **(C)** EWS/FLI and KDM1A knockdown or **(E)** KDM1A knockdown and SP-2509 treatment. **(F)** GSEA from RNA-seq experiments comparing SP-2509 treatment (rank-ordered dataset) and KDM1A knockdown in A673 cells. Normalized enrichment scores (NES) and *P* values are shown.