Table S1. Pathway analysis of genes bound by FOXO1 exclusively in the absence of a canonical FOXO1 binding motif

TermID	Term	Enrichment	logP	Genes in Term	Target Genes in Term	Fraction of Targets in Term	Total Target Genes	Total Genes	Gene Symbols
R-HSA-1442490	Collagen degradation	3.84E-05	-10.17	29	7	0.03	228	6734	MMP12, FURIN, MMP14, CTSD, COL25A1, MMP7, COL13A1
R-HSA-1474244	Extracellular matrix organization	1.15E-03	-6.77	219	17	0.07	228	6734	FGF2, BMP4, CTSD, ITGA11, COL25A1, MMP7, LAMC1, FURIN, DDR2, PCOLCE2, PPIB, COL13A1, MMP12, COL6A3, LAMA1, MFAP3, MMP14
R-HSA-1474228	Degradation of the extracellular matrix	2.82E-03	-5.87	72	8	0.04	228	6734	CTSD, MMP12, COL13A1, LAMC1, FURIN, MMP14, COL25A1, MMP7
R-HSA-3371453	Regulation of HSF1-mediated heat shock response	4.69E-03	-5.36	62	7	0.03	228	6734	HSPA1B, DNAJB6, YWHAE, HSPA9, HSPA7, NUP35, GSK3B
R-HSA-983712	Ion channel transport	8.14E-03	-4.81	122	10	0.04	228	6734	TRPM6, ATP7B, SGK1, ATP1A1, ANO6, ATP6V1B2, UBC, ATP9B, TRPV4, ATP11B
R-HSA-4641262	Disassembly of the destruction complex and recruitment of AXIN to the membrane	9.25E-03	-4.68	25	4	0.02	228	6734	CAV1, FZD5, GSK3B, PPP2R5E
R-HSA-2173793	Transcriptional activity of SMAD2/SMAD3:SMAD4 heterotrimer	1.31E-02	-4.34	42	5	0.02	228	6734	TGIF1, CCNK, UBC, WWTR1, SKI
R-HSA-3371556	Cellular response to heat stress	1.71E-02	-4.07	79	7	0.03	228	6734	DNAJB6, HSPA1B, HSPA7, HSPA9, YWHAE, GSK3B, NUP35
R-HSA-2173796	SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription	1.76E-02	-4.04	30	4	0.02	228	6734	TGIF1, UBC, CCNK, WWTR1
R-HSA-1592389	Activation of Matrix Metalloproteinases	1.83E-02	-4.00	17	3	0.01	228	6734	MMP14, FURIN, MMP7
R-HSA-425393	Transport of inorganic cations/anions and amino acids/oligopeptides	1.92E-02	-3.95	63	6	0.03	228	6734	SLC4A7, SLC5A12, SLC4A2, SLC7A11, SLC43A2, SLC7A6
R-HSA-382551	Transmembrane transport of small molecules	2.25E-02	-3.80	437	23	0.10	228	6734	SLC5A12, SLC4A7, TRPM6, SLC7A11, ANO6, ATP1A1, SLC39A14, RNASEL, SGK1, NUP35, SLC39A8, ATP11B, DERL1, ATP9B, SLC7A6, SLC29A1, ATP7B, SLC4A2, ADD1, UBC, ATP6V1B2, TRPV4, SLC43A2
R-HSA-933541	TRAF6 mediated IRF7 activation	2.49E-02	-3.69	19	3	0.01	228	6734	TRAF6, IFIH1, TANK
R-HSA-170834	Signaling by TGF-beta Receptor Complex	2.69E-02	-3.61	68	6	0.03	228	6734	SKI, WWTR1, FURIN, CCNK, UBC, TGIF1
R-HSA-425381	Bicarbonate transporters	2.79E-02	-3.58	8	2	0.01	228	6734	SLC4A2, SLC4A7
R-HSA-442380	Zinc influx into cells by the SLC39 gene family	2.79E-02	-3.58	8	2	0.01	228	6734	SLC39A8, SLC39A14
R-HSA-5654726	Negative regulation of FGFR1 signaling	2.85E-02	-3.56	20	3	0.01	228	6734	SPRY2, FGF2, UBC
R-HSA-210991	Basigin interactions	2.85E-02	-3.56	20	3	0.01	228	6734	SLC7A11, SLC7A6, CAV1
R-HSA-5654733	Negative regulation of FGFR4 signaling	3.25E-02	-3.43	21	3	0.01	228	6734	SPRY2, UBC, FGF2
R-HSA-5654732	Negative regulation of FGFR3 signaling	3.25E-02	-3.43	21	3	0.01	228	6734	UBC, FGF2, SPRY2

Table S2. Pathway analysis of genes bound by FOXO1 exclusively in the presence of a canonical FOXO1 binding motif

TermID	Term	Enrichment	logP	Genes in Term	Target Genes in Term	Fraction of Targets in Term	Total Target Genes	Total Genes	Gene Symbols
R-HSA-8848021	Signaling by PTK6	1.09E-04	-9.12	55	17	0.02	787	6734	RASAL2, ARHGAP35, SOCS3, EGFR, SPRED1, PTPN1, KHDRBS3, BCAR1, NRG2, RASA3, RASA2, EPAS1, DOK1, LRRK2, BTC, NR3C1, UBB
R-HSA-162582	Signal Transduction	1.95E-04	-8.54	1409	204	0.26	787	6734	ARHGAP21, TCF7L2, BMP2, DNM3, CYP26B1, AGO2, RGS3, HSPG2, JUNB, ZFYVE9, NR3C1, FUZ, AXIN2, RARG, AKT3, IRS1, EEF2K, PTEN, FMNL2, ADAM10, PDE4B, GLI2, RHOB, PRKCD, CALM2, BIRC3, PTPRJ, WASF2, DUSP4, PPM1A, TRIO, WNT5A, KHDRBS3, TGFBR1, GNA13, BCL2L11, RHOBTB1, CXCR5, IGF1, CAMK2D, ZNRF3, GNG12, ROR1, TAX1BP1, NRP2, ESR1, PTK2, ADCY1, NCAM1, CDC42EP3, MDM2, PHLPP1, DGKI, PDE4D, ANGPT1, REEP5, BRAP, HNRNPM, CDK1, FGFBP3, RASA2, MYC, CENPP, LRRK2, DOK1, CAB39, RTN4, INSR, PRR5, RHEB, MYLK, WWOX, BDKRB2, SMAD7, E2F3, PDE1A, TSC1, BUB3, NRG2, DUSP10, BCAR1, BTC, INCENP, MYH9, RAF1, PTCH1, AMOTL1, EPAS1, RHOU, PAG1, MST1R, BMPR1A, MAPKAP1, ARHGDIB, PTPN1, SAV1, FLRT2, CTNNB1, AGTR1, STK11, RASAL2, HSP90AA1, ITGB3, ARHGAP26, ATP2A2, AKAP9, GRK6, INHBB, RHOT1, AP2A1, LRIG1, ARHGAP1, UBB, CDC14B, RPS6KA5, ARHGAP17, NCK1, MKL1, ALDH1A3, UBE2D3, LRP1, ARHGEF12, REEP3, NF2, NEDD4L, FAM13A, GRB10, DHRS3, PREX1, ARHGAP12, ANXA1, RAPGEF1, ARHGAP35, NDEL1, KAT2B, NFKB1, RSPO3, ABCA4, HDAC7, WIPF1, NTRK2, RICTOR, JAK1, THBS1, PPP3CC, PTGER2, STRAP, ROR2, NR4A1, DUSP6, ARHGEF37, PLB1, PIK3R1, ARRB1, FLT1, PSME4, SPRED1, LDLR, DAAM1, YWHAQ, SOCS3, PSMD9, RGS10, OTUD7B, VAV3, TLE1, RALGDS, PIK3CD, ARHGAP24, CDC14A, JUP, PPP1R12A, ABR, IGF1R, GFRA2, MAPKAPK2, RASA3, PDGFC, WWP1, PPP1R12B, ATP6V1C2, STAT1, APP, HIST1H2AC, EGFR, ARHGEF10, BCR, CILP, RALBP1, PLA2G4A, FOXO1, PDE8A, NGF, NFATC1, SQSTM1, PPP1R15A, ARHGEF3, PKN2, PDHB, GNA12, HDAC9, IL6ST, TRIM33, ADRB2
R-HSA-909733	Interferon alpha/beta signaling	1.41E-03	-6.57	45	13	0.02	787	6734	IRF1, JAK1, PTPN1, IFIT2, ISG20, IFIT1, STAT1, GBP2, HLA-C, ADAR, XAF1, IRF4, SOCS3
R-HSA-5218920	VEGFR2 mediated vascular permeability	1.92E-03	-6.26	26	9	0.01	787	6734	HSP90AA1, VAV3, CALM2, PRR5, JUP, AKT3, CTNNB1, RICTOR, MAPKAP1
R-HSA-6785807	Interleukin-4 and 13 signaling	2.02E-03	-6.20	75	18	0.02	787	6734	IRF4, SOCS3, HSP90AA1, FOS, FOXO1, RORC, RHOU, STAT1, VCAM1, ANXA1, PIK3R1, JUNB, MYC, F13A1, COL1A2, JAK1, RORA, CD36
R-HSA-194840	Rho GTPase cycle	2.14E-03	-6.15	112	24	0.03	787	6734	RHOT1, ARHGAP24, ARHGAP21, ABR, ARHGAP1, ARHGAP17, TRIO, ARHGEF12, GNA13, ARHGEF37, RHOBTB1, ARHGEF3, FAM13A, RHOU, PREX1, ARHGAP12, ARHGEF10, ARHGDIB, BCR, VAV3, RALBP1, ARHGAP35, RHOB, ARHGAP26
R-HSA-166520	Signalling by NGF	2.33E-03	-6.06	381	63	0.08	787	6734	BCL2L11, ARHGEF3, BTC, ARHGEF37, GNA13, RAF1, PIK3R1, SQSTM1, DUSP10, NR4A1, DUSP6, NRG2, TRIO, NGF, RICTOR, PDE1A, DUSP4, JAK1, NTRK2, PHLPP1, AKAP9, RALGDS, PIK3CD, MDM2, ITGB3, NCAM1, RASAL2, VAV3, ADCY1, PSMD9, MAPKAP1, SPRED1, PSME4, PTK2, CAMK2D, ARRB1, RASA2, BRAP, ARHGEF12, AGO2, MAPKAPK2, RASA3, GFRA2, DNM3, ANGPT1, UBB, RPS6KA5, ABR, AP2A1, FOXO1, CALM2, NFKB1, PRR5, PRKCD, RAPGEF1, PTEN, INSR, ARHGEF10, IRS1, PREX1, EGFR, AKT3, RTN4
R-HSA-1474244	Extracellular matrix organization	4.36E-03	-5.43	219	39	0.05	787	6734	COL5A2, NTN4, BMP2, COL19A1, HTRA1, COL1A2, MUSK, CD47, ITGB5, HSPG2, TNC, LOXL4, VCAM1, COL11A1, PLOD2, COL3A1, ADAM10, TNXB, MMP16, DCN, ACAN, PSEN1, THBS1, ADAMTS3, COL12A1, ITGB4, ASPN, TIMP2, CAST, CAPN2, DST, P4HA3, SPARC, ITGA5, COL15A1, COL2A1, EFEMP1, ITGB3, NCAM1
R-HSA-4411364	Binding of TCF/LEF:CTNNB1 to target gene promoters	4.84E-03	-5.33	7	4	0.01	787	6734	CTNNB1, MYC, AXIN2, TCF7L2
R-HSA-74713	IRS activation	5.81E-03	-5.15	4	3	0.00	787	6734	INSR, IRS1, GRB10
R-HSA-1483257	Phospholipid metabolism	6.51E-03	-5.03	155	29	0.04	787	6734	INPP5F, MTMR14, RARRES3, CHKA, LPCAT1, PLA2R1, MBOAT7, MTMR3, ALDH7A1, PLEKHA1, PITPNB, TNFAIP8L3, ETNK1, PNPLA7, MTMR7, AGPAT4, STARD10, PLB1, PIK3R1, TNFAIP8, CHDH, PGS1, PTEN, INPP4A, ABHD4, LCLAT1, PIK3CD, PLA2G4A, PTDSS2
R-HSA-186763	Downstream signal transduction	6.56E-03	-5.03	274	46	0.06	787	6734	PTK2, PSME4, SPRED1, MAPKAP1, ARRB1, CAMK2D, NCAM1, MDM2, ITGB3, PIK3CD, AKAP9, PHLPP1, PSMD9, ADCY1, RASAL2, JAK1, PDE1A, DUSP4, RICTOR, PIK3R1, RAF1, BTC, NRG2, DUSP6, BCAR1, NR4A1, DUSP10, INSR, AKT3, IRS1, EGFR, STAT1, PRKCD, PRR5, CALM2, FOXO1, PTEN, RAPGEF1, NCK1, ANGPT1, UBB, GFRA2, RASA2, RASA3, AGO2, BRAP
R-HSA-187037	NGF signalling via TRKA from the plasma membrane	7.07E-03	-4.95	304	50	0.06	787	6734	AKT3, EGFR, IRS1, INSR, PTEN, RAPGEF1, PRKCD, PRR5, CALM2, FOXO1, AP2A1, RPS6KA5, UBB, ANGPT1, DNM3, GFRA2, RASA3, MAPKAPK2, AGO2, BRAP, RASA2, ARRB1, CAMK2D, PTK2, PSME4, SPRED1, MAPKAP1, PSMD9, ADCY1, RASAL2, ITGB3, NCAM1, MDM2, PIK3CD, RALGDS, PHLPP1, AKAP9, NTRK2, PDE1A, JAK1, DUSP4, RICTOR, NGF, NRG2, DUSP6, NR4A1, DUSP10, RAF1, PIK3R1, BTC
R-HSA-877300	Interferon gamma signaling	7.93E-03	-4.84	66	15	0.02	787	6734	TRIM25, SOCS3, IRF4, HLA-C, TRIM8, NCAM1, PRKCD, STAT1, CAMK2D, PML, GBP2, IRF1, JAK1, VCAM1, PTPN1
R-HSA-622312	Inflammasomes	8.43E-03	-4.78	12	5	0.01	787	6734	HSP90AB1, TXNIP, APP, P2RX7, NLRP1
R-HSA-2468052	Establishment of Sister Chromatid Cohesion	8.80E-03	-4.73	8	4	0.01	787	6734	STAG2, RAD21, PDS5B, STAG1
R-HSA-5689896	Ovarian tumor domain proteases	9.05E-03	-4.70	32	9	0.01	787	6734	ZRANB1, TNIP1, NOD1, ESR1, YOD1, UBB, PTEN, OTUD7B, TRIM25
R-HSA-8856825	Cargo recognition for clathrin-mediated endocytosis	9.82E-03	-4.62	80	17	0.02	787	6734	EGFR, ARRB1, LDLR, STON2, SCARB2, AGTR1, ADRB2, DAB2, FCHO2, LDLRAP1, AP2A1, TOR1A, SLC2A8, UBB, SGIP1, WNT5A, PICALM
R-HSA-186797	Signaling by PDGF	1.00E-02	-4.60	295	48	0.06	787	6734	RASA3, AGO2, BRAP, PDGFC, RASA2, NCK1, UBB, ANGPT1, GFRA2, PTEN, RAPGEF1, PRKCD, PRR5, CALM2, FOXO1, AKT3, IRS1, EGFR, STAT1, INSR, NRG2, DUSP6, BCAR1, DUSP10, NR4A1, RAF1, PIK3R1, BTC, THBS1, DUSP4, JAK1, PDE1A, RICTOR, PSMD9, ADCY1, RASAL2, NCAM1, MDM2, ITGB3, PIK3CD, AKAP9, PHLPP1, ARRB1, CAMK2D, PTK2, PSME4, SPRED1, MAPKAP1
R-HSA-400206	Regulation of lipid metabolism by Peroxisome proliferator-activated receptor alpha (PPARalpha)	1.12E-02	-4.49	107	21	0.03	787	6734	NPAS2, CARM1, SREBF1, ABCB4, ARNT, ARNTL, MED15, SLC27A1, NR1D1, SIN3A, MED25, MED28, RORA, CD36, THRAP3, RGL1, FADS1, MED9, FDFT1, MED30, MED26

Table S3. Pathway analysis of genes bound by FOXO1 exclusively at enhancer regions

TermID	Term	Enrichment	logP	Genes in Term	Target Genes in Term	Fraction of Targets in Term	Total Target Genes	Total Genes	Gene Symbols
R-HSA-1474244	Extracellular matrix organization	5.38E-09	-19.04	219	53	0.07	721	6734	VCAM1,NTN4,TIMP2,COL5A2,HSPG2,MMP7,CAST,ITGB4,COL6A3,P4HA3,MMP14,LAMA1,LTBP2,SPARC,THBS1,LTBP1,HAPLN1,COL13A1,ITGA11,ADAMTS5,FGF2,TNC,COL15A1,COL11A1,PCOLCE2,ADAMTS9,NCAM1,COL2A1,COL25A1,HTRA1,FURIN,DDR2,ITGA5,VCAN,ITGB5,MMP16,DST,ADAM10,TNXB,MUSK,ITGB3,BMP4,ITGB1,ACAN,COL19A1,MFAP3,MMP12,ADAMTS3,LUM,FBLN1,PPIB,PSEN1,ASPN
R-HSA-3000178	ECM proteoglycans	2.09E-04	-8.48	46	14	0.02	721	6734	ITGB3,HAPLN1,ITGB1,TNC,NCAM1,ACAN,ASPN,LAMA1,VCAN,ITGB5,LUM,SPARC,MUSK,TNXB
R-HSA-1474228	Degradation of the extracellular matrix	4.31E-04	-7.75	72	18	0.02	721	6734	CAST,MMP7,MMP12,COL19A1,ACAN,TIMP2,ADAM10,MMP16,HSPG2,COL15A1,COL13A1,ADAMTS5,FURIN,PSEN1,ADAMTS9,HTRA1,COL25A1,MMP14
R-HSA-1368108	BMAL1:CLOCK,NPAS2 activates circadian gene expression	1.38E-03	-6.59	43	12	0.02	721	6734	PPARGC1A,CHD9,BHLHE40,RXRA,KLF15,NPAS2,NRIP1,BHLHE41,PER1,NR1D1,NR3C1,ARNTL
R-HSA-190377	FGFR2b ligand binding and activation	1.64E-03	-6.41	6	4	0.01	721	6734	FGF2,FGF1,FGFR2,FGFBP3
R-HSA-162582	Signal Transduction	1.77E-03	-6.34	1409	182	0.25	721	6734	PTPN1,PIK3CB,ABL1,PDE8A,RARG,TNFRSF1A,ARHGAP42,CCL28,WWTR1,AKR1C1,JAK1,PPP1R15A,GNAQ,PPP3CC,BCAR1,INTU,PDGFC,PDHB,NTRK2,NET1,DGKI,RHOBTB1,YWHAQ,PTGER2,PPP2R5E,PSMD9,FZD5,CD55,NEDD4L,PPP1R12A,PAG1,DNM3,ROR2,GRB10,PRKAB2,NFKB1,TRIO,TRIM33,MYLK,ARRB1,ARHGAP22,LRIG1,SOCS3,ABCA4,CYP26B1,RHOU,FSTL1,AKT3,RICTOR,PRKCD,PDGFRA,ARHGAP12,PLA2G4A,CTNNB1,RXRA,ITGB3,WIPF1,RALGDS,MYH9,ROR1,RTN4,ADAM10,SPRED1,CAMK2D,AGTR1,RGS3,FURIN,RASAL2,KHDRBS3,TCF7L2,ANXA1,BDKRB2,FGF2,SMAD7,CDC14A,THBS1,CDH5,BCR,RASA3,LAMA1,GRIN2A,CDKN2B,CCNK,FGF1,SMAD6,MAPKAP1,RHOB,NRP2,TAX1BP1,HNRNPM,RBFOX2,CDC14B,ARHGDIB,EPAS1,GLI2,STRAP,INHBA,EEF2K,NR3C1,ARHGAP17,ADRB2,MEF2C,INCENP,TLE3,HDAC7,DUSP10,RAPGEF1,ARHGEF10,NCAM1,CAB39,FGFR2,PLB1,STAT1,TIAM2,AMOTL1,ZNRF3,IL6ST,ANGPT1,CAV1,VAV3,WNT5A,WWOX,GFRA2,COL6A3,ATP6V1B2,ZFYVE9,NR4A1,RSPO3,HSPG2,TRAF6,GNG12,SAV1,RHEB,NDEL1,ARHGEF3,RAPGEF2,RGS1,GPC6,ATP2A2,TGIF1,FGFBP3,AXIN2,DOK1,STARD13,SQSTM1,TGFBR1,GNA12,UBB,E2F3,RAP1B,TNRC6B,CDC42EP3,DIAPH1,ALDH1A3,NFATC1,JUP,MST1R,ITGB1,SOX6,PDE4B,NOTCH2,IGF1,ARHGEF12,EGFR,PKN2,PTEN,ATP6V1C2,FLT1,ARHGAP35,ABR,DLC1,IRS1,AGO2,CENPP,RAF1,CDON,SPOPL,RARB,GAS1,WWP1,DAAM1,MAPKAPK2
R-HSA-3000171	Non-integrin membrane-ECM interactions	1.97E-03	-6.23	39	11	0.02	721	6734	ITGB4,ITGB1,FGF2,TNC,ITGB3,NTN4,ITGB5,LAMA1,DDR2,THBS1,HSPG2
R-HSA-983712	Ion channel transport	2.19E-03	-6.12	122	24	0.03	721	6734	UBB,NEDD4L,STOM,ATP7B,ATP8B1,ANO6,ATP11B,SCNN1A,ATP2B4,MCOLN2,TRPM6,CAMK2D,ANO1,TPCN1,ATP9A,ATP6V1C2,ATP2A2,TRPV4,RAF1,ATP8B4,TTYH3,ATP6V1B2,ATP1A1,WWP1
R-HSA-1442490	Collagen degradation	2.44E-03	-6.02	29	9	0.01	721	6734	ADAM10,MMP14,FURIN,MMP12,COL19A1,COL25A1,COL15A1,COL13A1,MMP7
R-HSA-3000170	Syndecan interactions	2.49E-03	-6.00	19	7	0.01	721	6734	ITGB3,ITGB5,TNC,ITGB4,FGF2,ITGB1,THBS1
R-HSA-1566948	Elastic fibre formation	2.82E-03	-5.87	35	10	0.01	721	6734	ITGB5,LTBP2,ITGA5,ITGB3,BMP4,LTBP1,ITGB1,FBLN1,MFAP3,FURIN
R-HSA-400253	Circadian Clock	2.99E-03	-5.81	65	15	0.02	721	6734	BHLHE41,PER1,RXRA,NPAS2,KLF15,NRIP1,BHLHE40,PPARGC1A,CHD9,ARNTL,UBB,NR3C1,NR1D1,MEF2C,SREBF1
R-HSA-2129379	Molecules associated with elastic fibres	3.42E-03	-5.68	25	8	0.01	721	6734	FBLN1,MFAP3,LTBP1,ITGB3,BMP4,ITGB1,LTBP2,ITGB5
R-HSA-190241	FGFR2 ligand binding and activation	3.50E-03	-5.66	7	4	0.01	721	6734	FGFR2,FGFBP3,FGF1,FGF2
R-HSA-8848021	Signaling by PTK6	4.46E-03	-5.41	55	13	0.02	721	6734	SOCS3,RASA3,EGFR,NR3C1,SPRED1,UBB,BCAR1,RASAL2,KHDRBS3,DOK1,EPAS1,PTPN1,ARHGAP35
R-HSA-5218920	VEGFR2 mediated vascular permeability	4.48E-03	-5.41	26	8	0.01	721	6734	CAV1,VAV3,AKT3,CDH5,RICTOR,MAPKAP1,JUP,CTNNB1
R-HSA-190375	FGFR2c ligand binding and activation	4.50E-03	-5.40	4	3	0.00	721	6734	FGF1,FGF2,FGFR2
R-HSA-3781865	Diseases of glycosylation	5.01E-03	-5.30	62	14	0.02	721	6734	ADAMTS6,THSD4,ACAN,ADAMTSL3,ADAMTS9,ADAMTS5,PRELP,NOTCH2,THBS1,HSPG2,LUM,GPC6,VCAN,ADAMTS3
R-HSA-381340	Transcriptional regulation of white adipocyte differentiation	5.07E-03	-5.28	75	16	0.02	721	6734	SREBF1,KLF4,MED30,MED27,CHD9,RXRA,CD36,NFKB1,MED4,MED15,MED9,EBF1,PPARGC1A,MED26,THRAP3,EGR2
R-HSA-1266738	Developmental Biology	5.77E-03	-5.16	637	88	0.12	721	6734	ABL1,EGR2,EPAS1,PIK3CB,SIAH2,MEF2C,RARG,CACNB2,ANK2,CHD9,JAK1,KLF4,SREBF1,PPL,ITGA5,MYO10,DUSP10,HSP90AB1,PPP2R5E,PSMD9,PPARGC1A,EBF1,NCAM1,FGFR2,THRAP3,ANGPT1,VAV3,DNM3,DPYSL2,GRB10,ANK1,SEMA6D,MED15,ARRB1,MED4,NFKB1,TRIO,GFRA2,COL6A3,RAPGEF2,FOXP1,TCF12,MED30,DOK1,UBB,AKT3,EPHA3,RAP1B,ITGB3,NEO1,MYH9,ITGB1,PDGFRA,ANK3,CD36,JUP,CTNNB1,RXRA,EGFR,PLXNA4,SLIT2,ARHGEF12,EFNA5,ADAM10,CAMK2D,SPRED1,RASAL2,MED26,FGF2,PTPRC,ARHGAP35,FURIN,ARHGEF28,RASA3,LAMA1,GRIN2A,IRS1,MED9,RARB,STX1A,FGF1,RAF1,CDON,ENAH,NTN4,MED27,RHOB,NRP2

Table S4. Pathway analysis of genes bound by FOXO1 exclusively at promoter regions

TermID	Term	Enrichment	logP	Genes in Term	Target Genes in Term	Fraction of Targets in Term	Total Target Genes	Total Genes	Gene Symbols
R-HSA-622312	Inflammasomes	2.89E-03	-5.85	12	3	0.02	169	6734	TXNIP, NLRP1, P2RX7
R-HSA-2262752	Cellular responses to stress	9.57E-03	-4.65	364	17	0.10	169	6734	GABARAPL1, HSPA1B, ARNT, TERF2IP, GSTP1, BAG1, HSP90AA1, WIPI2, SOD1, TSC1, MTMR14, MAPK7, HSPA13, CDKN2D, HSPA9, MDM2, MAP2K3
R-HSA-6785807	Interleukin-4 and 13 signaling	1.10E-02	-4.51	75	6	0.04	169	6734	RORA, HSP90AA1, RORC, JUNB, FOXO1, CCL2
R-HSA-381753	Olfactory Signaling Pathway	1.21E-02	-4.41	7	2	0.01	169	6734	REEP3, REEP5
R-HSA-198753	ERK/MAPK targets	1.48E-02	-4.21	21	3	0.02	169	6734	MAPK7, RPS6KA5, DUSP4
R-HSA-975138	TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	1.57E-02	-4.15	81	6	0.04	169	6734	MAP2K3, MAPK7, RPS6KA5, CD14, DUSP4, HMGB1
R-HSA-2468052	Establishment of Sister Chromatid Cohesion	1.59E-02	-4.14	8	2	0.01	169	6734	STAG2, RAD21
R-HSA-168181	Toll Like Receptor 7/8 (TLR7/8) Cascade	1.76E-02	-4.04	83	6	0.04	169	6734	MAP2K3, CD14, RPS6KA5, MAPK7, HMGB1, DUSP4
R-HSA-975155	MyD88 dependent cascade initiated on endosome	1.76E-02	-4.04	83	6	0.04	169	6734	DUSP4, HMGB1, CD14, MAPK7, RPS6KA5, MAP2K3
R-HSA-166058	MyD88:Mal cascade initiated on plasma membrane	1.95E-02	-3.94	85	6	0.04	169	6734	DUSP4, HMGB1, MAPK7, RPS6KA5, CD14, MAP2K3
R-HSA-181438	Toll Like Receptor 2 (TLR2) Cascade	1.95E-02	-3.94	85	6	0.04	169	6734	MAPK7, RPS6KA5, CD14, MAP2K3, HMGB1, DUSP4
R-HSA-168179	Toll Like Receptor TLR1:TLR2 Cascade	1.95E-02	-3.94	85	6	0.04	169	6734	DUSP4, HMGB1, MAP2K3, RPS6KA5, MAPK7, CD14
R-HSA-168188	Toll Like Receptor TLR6:TLR2 Cascade	1.95E-02	-3.94	85	6	0.04	169	6734	MAP2K3, MAPK7, CD14, RPS6KA5, HMGB1, DUSP4
R-HSA-844456	The NLRP3 inflammasome	2.01E-02	-3.91	9	2	0.01	169	6734	TXNIP, P2RX7
R-HSA-2470946	Cohesin Loading onto Chromatin	2.01E-02	-3.91	9	2	0.01	169	6734	STAG2, RAD21
R-HSA-425393	Transport of inorganic cations/anions and amino acids/oligopeptides	2.04E-02	-3.89	63	5	0.03	169	6734	SLC38A2, CALM2, SLC12A6, SLC7A11, SLC4A2
R-HSA-168138	Toll Like Receptor 9 (TLR9) Cascade	2.06E-02	-3.88	86	6	0.04	169	6734	HMGB1, DUSP4, CD14, RPS6KA5, MAPK7, MAP2K3
R-HSA-198725	Nuclear Events (kinase and transcription factor activation)	2.13E-02	-3.85	24	3	0.02	169	6734	RPS6KA5, MAPK7, DUSP4
R-HSA-5674400	Constitutive Signaling by AKT1 E17K in Cancer	2.38E-02	-3.74	25	3	0.02	169	6734	GSK3A, MDM2, FOXO1
R-HSA-381042	PERK regulates gene expression	2.64E-02	-3.63	26	3	0.02	169	6734	EIF2AK3, EXOSC2, CCL2

Table S5. Pathway analysis of the 147 FOXO1 putative genes shared by all 4 cell types

TermID	Term	Enrichment	logP	Genes in Term	Target Genes in Term	Fraction of Targets in Term	Total Target Genes	Total Genes	Gene Symbols
R-HSA-450282	MAPK targets/ Nuclear events mediated by MAP kinases	5.75E-05	-9.76	31	4	0.06	72	10411	FOS, MEF2A, DUSP4, DUSP6
R-HSA-166520	Signalling by NGF	9.69E-05	-9.24	479	12	0.17	72	10411	DUSP4, DUSP6, TNRC6B, RAPGEF1, FGD4, PIK3CB, MEF2A, PTK2, RALGDS, VAV3, PIK3R1, JAK1
R-HSA-2454202	Fc epsilon receptor (FCERI) signaling	2.54E-04	-8.28	378	10	0.14	72	10411	DUSP6, TNRC6B, DUSP4, NFATC1, PIK3CB, PTK2, FOS, JAK1, VAV3, PIK3R1
R-HSA-187037	NGF signalling via TRKA from the plasma membrane	3.07E-04	-8.09	387	10	0.14	72	10411	PTK2, PIK3R1, RALGDS, JAK1, DUSP4, TNRC6B, DUSP6, PIK3CB, RAPGEF1, MEF2A
R-HSA-2029480	Fcgamma receptor (FCGR) dependent phagocytosis	4.91E-04	-7.62	95	5	0.07	72	10411	PTK2, MYH9, VAV3, PIK3R1, PIK3CB
R-HSA-114604	GPVI-mediated activation cascade	5.12E-04	-7.58	54	4	0.06	72	10411	VAV3, PIK3R1, PIK3CB, JAK1
R-HSA-450294	MAP kinase activation in TLR cascade	9.77E-04	-6.93	64	4	0.06	72	10411	DUSP6, DUSP4, FOS, MEF2A
R-HSA-6806834	Signaling by MET	1.30E-03	-6.65	69	4	0.06	72	10411	PTK2, PTPN1, PIK3R1, RAPGEF1
R-HSA-166016	Toll Like Receptor 4 (TLR4) Cascade	1.76E-03	-6.34	126	5	0.07	72	10411	DUSP4, DUSP6, MEF2A, FOS, CD180
R-HSA-1266738	Developmental Biology	2.40E-03	-6.03	1078	16	0.22	72	10411	DUSP6, DUSP4, EBF1, MEF2A, SMAD3, PIK3CB, FOXP1, PTK2, RBPJ, DPYSL2, VAV3, PIK3R1, ANK3, MED9, JAK1, MYH9

Table S6. Pathway analysis using KeggDB of the 428 genes bound by FOXO1 and DE in OA

TermID	Term	Enrichment	logP	Genes in Term	Target Genes in Term	Fraction of Targets in Term	Total Target Genes	Total Genes	Gene Symbols
hsa04710	Circadian rhythm	6.65E-04	-7.32	12	7	0.04	178	1174	NR1D1, BHLHE40, RORC, NPAS2, PER1, ARNTL, BHLHE41
hsa04974	Protein digestion and absorption	8.15E-04	-7.11	19	9	0.05	178	1174	COL3A1, COL13A1, COL5A2, COL6A3, COL1A2, COL15A1, COL2A1, MME, DPP4
ko04512	ECM-receptor interaction	1.42E-03	-6.55	24	10	0.06	178	1174	ITGB5, ITGB3, ITGB8, THBS2, TNC, ITGB4, COL1A2, SPP1, COL6A3, COL2A1
ko05224	Breast cancer	4.55E-03	-5.39	36	12	0.07	178	1174	FZD8, FZD10, MYC, WNT11, CCND1, FOS, WNT5A, FGF1, CDK6, CDKN1A, HES1, FZD5
hsa_M00677	Wnt signaling	5.70E-03	-5.17	9	5	0.03	178	1174	WNT11, FZD10, FZD8, WNT5A, FZD5
ko05219	Bladder cancer	7.60E-03	-4.88	13	6	0.03	178	1174	CCND1, CDKN1A, MMP2, MYC, DAPK2, RPS6KA5
ko05166	HTLV-I infection	9.03E-03	-4.71	58	16	0.09	178	1174	ATF3, FOS, WNT11, FZD10, FZD8, TLN2, ADCY1, ZFP36, VCAM1, CDKN2B, WNT5A, CCND1, MYC, CDKN1A, FZD5, ETS2
ko04151	PI3K-Akt signaling pathway	1.50E-02	-4.20	87	21	0.12	178	1174	CCND1, TNC, MYC, NR4A1, PDGFC, THBS2, ITGB8, CDKN1A, COL1A2, CDK6, IL6R, NGF, SPP1, ITGB5, ITGB3, SGK1, COL2A1, CDKN1B, ITGB4, COL6A3, FGF1
hsa05412	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	1.64E-02	-4.11	19	7	0.04	178	1174	ITGB5, ITGB4, CDH2, JUP, ITGB8, ITGB3, SGCD
hsa04115	p53 signaling pathway	1.64E-02	-4.11	19	7	0.04	178	1174	CDKN1A, CDK1, CCND1, GADD45A, GADD45B, IGFBP3, CDK6
ko04110	Cell cycle	1.66E-02	-4.10	37	11	0.06	178	1174	WEE1, MYC, CDK1, CCND1, CDKN2B, CDK6, CDKN1A, GADD45A, BUB1, GADD45B, CDKN1B
ko05217	Basal cell carcinoma	1.70E-02	-4.07	15	6	0.03	178	1174	FZD10, FZD8, WNT11, GLI3, FZD5, WNT5A
hsa04068	FoxO signaling pathway	1.78E-02	-4.03	47	13	0.07	178	1174	SGK1, S1PR1, BCL6, CCND1, CDKN2B, BNIP3, IRS2, GADD45B, CDKN1B, FBXO32, KLF2, CDKN1A, GADD45A
hsa00330	Arginine and proline metabolism	2.17E-02	-3.83	8	4	0.02	178	1174	ALDH2, ALDH1B1, P4HA3, ALDH3A2
ko00410	beta-Alanine metabolism	2.17E-02	-3.83	8	4	0.02	178	1174	AOC3, ALDH2, ALDH3A2, ALDH1B1
hsa00561	Glycerolipid metabolism	2.43E-02	-3.72	12	5	0.03	178	1174	LCLAT1, ALDH2, ALDH1B1, DGKI, ALDH3A2
hsa00053	Ascorbate and aldarate metabolism	2.71E-02	-3.61	5	3	0.02	178	1174	ALDH2, ALDH1B1, ALDH3A2
ko00620	Pyruvate metabolism	3.46E-02	-3.36	9	4	0.02	178	1174	ALDH2, ACSS1, ALDH1B1, ALDH3A2
hsa04713	Circadian entrainment	4.26E-02	-3.16	18	6	0.03	178	1174	NOS1AP, FOS, PER1, GRIN2A, RPS6KA5, ADCY1
hsa05205	Proteoglycans in cancer	4.82E-02	-3.03	64	15	0.08	178	1174	ITGB3, ITGB5, WNT11, MYC, FZD8, FZD10, TFAP4, CCND1, WNT5A, LUM, ANK3, FZD5, MMP2, TIMP3, CDKN1A