Classification of Primary and Secondary Response Genes in A549 Cells to Short-term Manganese Exposure: Bioinformatic Analysis and Experimental Verification

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. The list of Mn-induced PRGs

Gene name	Description	Mn vs. Control		CHX_Mn vs. Mn	
		Log_2FC	P-value	Log_2FC	P-value
LONRF3	LON peptidase N-terminal domain and ring finger 3	0.45	1.77E-02	0.44	1.79E-02
TOB2	transducer of ERBB2, 2	0.35	5.73E-04	0.49	3.64E-06
GDF15	growth differentiation factor 15	0.58	6.85E-03	1.02	1.70E-06
IL6R	interleukin 6 receptor	0.34	1.82E-02	1.41	1.95E-25
ITPRIP	inositol 1,4,5-trisphosphate receptor interacting protein	0.41	9.06E-04	1.45	1.90E-33
FLCN	folliculin	0.34	1.24E-02	0.27	3.99E-02
C11orf86	chromosome 11 open reading frame 86	0.27	1.62E-02	0.85	1.03E-12
LUCAT1	lung cancer associated transcript 1	0.51	4.67E-03	0.62	2.26E-03
CSRNP1	cysteine and serine rich nuclear protein 1	0.57	1.32E-05	2.84	1.88E-128
RNF223	ring finger protein 223	0.56	1.20E-02	2.82	4.25E-79
RRAD	RRAD, Ras related glycolysis inhibitor and calcium channel regulator	0.57	3.36E-02	1.30	7.57E-11
PMEPA1	prostate transmembrane protein, androgen induced 1	0.32	2.63E-02	0.93	4.94E-10
DCBLD1	discoidin, CUB and LCCL domain containing 1	0.29	2.58E-02	0.89	2.46E-11
PLAUR	plasminogen activator, urokinase receptor	0.52	9.45E-07	0.71	1.04E-09
ERRFI1	ERBB receptor feedback inhibitor 1	0.42	4.36E-03	2.38	7.16E-58
VEGFA	vascular endothelial growth factor A	0.68	1.17E-09	0.77	5.40E-08
SDC4	syndecan 4	0.28	3.77E-02	1.55	2.83E-32
ZNF426	zinc finger protein 426 [Source:HGNC Symbol; Acc:HGNC:20725]	0.27	3.21E-02	0.59	1.00E-05
CHD2	chromodomain helicase DNA binding protein 2	0.54	3.23E-04	1.82	4.21E-37
RELB	RELB proto-oncogene, NF-kB subunit	0.41	1.02E-02	2.03	5.47E-32
JUNB	JunB proto-oncogene, AP-1 transcription factor subunit	0.59	2.58E-08	1.00	1.53E-17
JUN	Jun proto-oncogene, AP-1 transcription factor subunit	0.59	1.38E-04	3.10	7.88E-85
SLC43A2	solute carrier family 43 member 2	0.33	1.81E-02	0.67	7.90E-07
SAAL1	serum amyloid A like 1	0.27	4.03E-02	0.62	2.51E-06
PER1	period circadian regulator 1	0.35	3.61E-02	0.79	1.21E-07
CARD10	caspase recruitment domain family member 10	0.33	1.14E-02	0.74	5.74E-10
CCNG2	cyclin G2	0.43	9.53E-03	0.34	4.49E-02
SMTN	smoothelin	0.30	9.66E-03	0.31	1.04E-02
SIK1	salt inducible kinase 1	0.48	3.52E-02	1.22	7.34E-03
MN1	MN1 proto-oncogene, transcriptional regulator	0.55	9.08E-05	1.44	2.14E-30
CSRP2	cysteine and glycine rich protein 2	0.32	2.92E-02	0.31	4.14E-02
ZCCHC2	zinc finger CCHC-type containing 2	0.35	2.43E-02	0.80	3.32E-05
SERTAD1	SERTA domain containing 1	0.47	3.17E-03	1.96	5.20E-42
NR1D1	nuclear receptor subfamily 1 group D member 1	0.38	1.38E-02	2.21	6.84E-67
ARRDC3	arrestin domain containing 3	1.11	7.03E-11	1.90	2.41E-36
GEM	GTP binding protein overexpressed in skeletal muscle	0.92	3.56E-02	2.28	4.65E-14

RHOB	ras homolog family member B	0.50	1.80E-07	1.65	4.63E-44
ZDHHC11B	zinc finger DHHC-type containing 11B	1.65	4.46E-02	1.54	2.21E-03
MALAT1	metastasis associated lung adenocarcinoma transcript 1	0.30	1.78E-02	0.48	1.25E-04
PHLDA2	pleckstrin homology like domain family A member 2	0.54	6.04E-06	0.30	1.60E-02
ULK1	unc-51 like autophagy activating kinase 1	0.33	1.81E-03	1.38	1.12E-25
BMP2	bone morphogenetic protein 2	0.29	1.63E-02	2.83	1.10E-107
SOX9	SRY-box 9	0.32	4.45E-02	1.75	2.56E-24
TTI2	TELO2 interacting protein 2	0.46	6.24E-03	0.54	6.44E-04
KDM3A	lysine demethylase 3A	0.61	1.07E-06	0.32	5.93E-03
CDKN1A	cyclin dependent kinase inhibitor 1A	0.84	3.17E-08	2.21	5.13E-67
ARID5A	AT-rich interaction domain 5A	0.75	4.31E-05	0.48	3.75E-02
PNRC1	proline rich nuclear receptor coactivator 1	0.34	1.42E-02	1.43	4.54E-26
RSRC2	arginine and serine rich coiled-coil 2 [Source:HGNC Symbol; Acc:HGNC:30559]	0.34	4.17E-02	1.47	4.33E-20
ZNF280C	zinc finger protein 280C	0.44	3.97E-02	1.33	3.01E-13
TRPV3	transient receptor potential cation channel subfamily V member 3	1.06	1.79E-02	3.32	1.03E-36
GTF2IP13	general transcription factor IIi pseudogene 13	0.35	4.76E-02	0.87	7.79E-07
TSC22D3	TSC22 domain family member 3	0.57	8.65E-05	0.49	2.15E-03
ZNF160	zinc finger protein 160	0.37	2.35E-02	0.65	3.06E-05
STC1	stanniocalcin 1	1.31	8.06E-08	0.93	1.94E-05
EIF4A2	eukaryotic translation initiation factor 4A2	0.27	1.38E-02	0.83	5.86E-12
ID3	inhibitor of DNA binding 3, HLH protein	0.43	9.57E-05	2.94	1.44E-121
SRSF6	serine and arginine rich splicing factor 6	0.31	3.76E-03	0.83	3.28E-13
NR4A1	nuclear receptor subfamily 4 group A member 1	0.56	4.96E-04	2.05	2.03E-50
SLC3A2	solute carrier family 3 member 2	0.28	4.15E-02	0.48	1.54E-04
MST1R	macrophage stimulating 1 receptor	0.28	1.91E-02	0.26	3.08E-02
IRAK2	interleukin 1 receptor associated kinase 2	0.52	8.05E-03	1.49	4.58E-18
MT-RNR2	mitochondrially encoded 16S RNA	0.84	3.16E-16	0.33	1.76E-03
PMP22	peripheral myelin protein 22	0.26	1.06E-02	0.58	2.94E-07
IER3	immediate early response 3	0.55	1.06E-06	1.96	1.42E-63
AC244154.1	aminopeptidase puromycin sensitive pseudogene	0.47	2.73E-02	0.51	2.22E-02
BTG1	BTG anti-proliferation factor 1	0.42	1.67E-03	1.63	2.21E-42
PTGS2	prostaglandin-endoperoxide synthase 2	0.87	7.65E-06	3.10	1.27E-103
IL11	interleukin 11	0.62	1.32E-03	3.80	1.38E-130
SLC41A2	solute carrier family 41 member 2	0.46	1.91E-02	0.96	9.92E-08
AKAP17A	A-kinase anchoring protein 17A	0.40	7.25E-04	0.79	3.00E-11
HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1	0.58	7.07E-03	0.69	5.94E-04
KDM6B	lysine demethylase 6B	0.39	1.15E-02	1.39	5.42E-24
AKAP8L	A-kinase anchoring protein 8 like	0.29	1.30E-02	0.47	1.65E-04
CXCR4	C-X-C motif chemokine receptor 4	0.41	1.57E-03	0.67	1.75E-06
NEU1	neuraminidase 1	0.35	1.72E-03	0.50	1.74E-04
ELF3	E74 like ETS transcription factor 3	0.52	2.77E-06	1.05	9.10E-17

CFAP69	cilia and flagella associated protein 69	0.87	1.51E-02	1.06	1.08E-04
ADPRHL1	ADP-ribosylhydrolase like 1	0.58	3.34E-05	1.73	9.48E-38
AL135905.2	Protein tyrosine phosphatase type IVA 1	0.41	1.12E-03	1.45	5.32E-25
ZNF562	zinc finger protein 562	0.27	4.49E-02	0.63	1.26E-06
CBX4	chromobox 4	0.36	6.77E-04	0.35	1.68E-03
STX1A	syntaxin 1A	0.35	3.72E-02	1.04	1.10E-10
EGR1	early growth response 1	1.02	4.53E-09	4.82	1.60E-275
ITGA5	integrin subunit alpha 5	0.62	9.37E-08	0.45	1.10E-03
SAMD8	sterile alpha motif domain containing 8	0.32	2.68E-02	1.28	3.19E-20
RCE1	Ras converting CAAX endopeptidase 1 [Source:HGNC Symbol; Acc:HGNC:13721]	0.34	4.48E-03	0.29	2.13E-02
DHRS3	dehydrogenase/reductase 3 [Source:HGNC Symbol; Acc:HGNC:17693]	0.72	7.94E-03	0.71	1.67E-03
SLC2A1	solute carrier family 2 member 1	0.50	5.29E-04	0.45	1.85E-03
METRNL	meteorin like, glial cell differentiation regulator	0.34	2.01E-03	0.85	5.50E-14
BHLHE40	basic helix-loop-helix family member e40	0.95	7.44E-21	1.16	3.12E-23
FOS	Fos proto-oncogene, AP-1 transcription factor subunit	0.99	7.29E-04	2.61	1.52E-12

Supplementary Table 2. The list of Mn-induced SRGs

Gene name	Description	Mn vs. Control		CHX_Mn vs. Mn	
		Log_2FC	P-value	Log_2FC	P-value
SHISAL1	shisa like 1	0.33	2.08E-02	-0.75	1.70E-05
MT-ND6	mitochondrially encoded NADH: ubiquinone oxidoreductase core subunit 6	0.42	6.43E-03	-0.47	5.71E-04
MVK	mevalonate kinase	0.60	4.38E-03	-0.43	2.18E-02
CHAC1	ChaC glutathione specific gamma-glutamyl cyclo transferase 1	1.10	2.45E-03	-2.29	4.95E-09
TRIB3	tribbles pseudokinase 3	0.43	1.07E-02	-1.95	1.76E-29
AC063976.2	cytoplasmic linker associated protein 2 (CLASP2) pseudogene	1.67	2.78E-02	-2.83	1.62E-03
TRAF5	TNF receptor associated factor 5	0.32	2.45E-02	-1.83	2.24E-23
USP31	ubiquitin specific peptidase 31	0.27	4.71E-02	-1.19	1.15E-17
AFAP1	actin filament associated protein 1	0.35	5.09E-03	-0.44	1.08E-03
SEMA3F	semaphorin 3F	0.31	1.22E-02	-1.06	3.26E-14
MSMO1	methylsterol monooxygenase 1	0.77	4.32E-04	-0.79	5.63E-05
NOTCH1	notch 1	0.30	2.37E-02	-0.59	1.53E-05
UBE2O	ubiquitin-conjugating enzyme E2 O	0.36	2.01E-03	-0.46	4.67E-04
DHCR7	7-dehydrocholesterol reductase	0.39	2.70E-02	-0.90	7.27E-08
PIM2	Pim-2 proto-oncogene, serine/threonine kinase	0.44	2.27E-02	-0.96	4.16E-07
MT-TL1	mitochondrially encoded tRNA leucine 1 (UUA/G)	0.92	1.88E-08	-0.33	4.78E-02
MAPK8IP1	mitogen-activated protein kinase 8 interacting protein 1	0.60	2.57E-02	-0.71	9.29E-03
FAM13A	family with sequence similarity 13 member A	0.37	4.78E-02	-1.05	3.24E-07
BNIP3L	BCL2 interacting protein 3 like	0.37	1.83E-02	-0.75	1.17E-06
FGFRL1	fibroblast growth factor receptor like 1	0.32	1.64E-02	-0.63	8.91E-06
PLEK2	pleckstrin 2	0.33	3.73E-02	-0.35	3.51E-02
HK2	hexokinase 2	0.60	3.19E-06	-0.47	2.97E-04
GL000220.1	PF13900:Putative domain of unknown function |PF12895:Anaphase-promoting complex, cyclosome, subunit 3 |PF13414:TPR repeat	0.80	1.53E-04	-0.59	3.50E-03
FA2H	fatty acid 2-hydroxylase	0.37	5.96E-03	-0.35	1.12E-02
NOD1	nucleotide binding oligomerization domain containing 1	0.40	5.90E-03	-1.55	1.33E-19
MT-TM	mitochondrially encoded tRNA methionine	1.32	3.78E-02	-2.03	5.03E-03
SMARCD3	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 3	0.30	4.61E-02	-1.13	8.75E-10
GRIN2D	glutamate ionotropic receptor NMDA type subunit 2D	0.38	5.84E-03	-0.43	3.94E-03
LMTK3	lemur tyrosine kinase 3	0.38	2.09E-02	-1.69	1.09E-16
MTATP6P1	MT-ATP6 pseudogene 1	0.33	2.19E-02	-0.44	5.56E-04
ABCB6	ATP binding cassette subfamily B member 6 (Langereis blood group)	0.52	3.98E-02	-2.13	4.47E-13
MT-TP	mitochondrially encoded tRNA proline	0.32	2.52E-03	-0.54	4.94E-06
MT-TE	mitochondrially encoded tRNA glutamic acid	1.65	7.99E-04	-1.14	1.63E-02

CISH	cytokine inducible SH2 containing protein	0.64	1.35E-03	-1.85	2.58E-16
PDK1	pyruvate dehydrogenase kinase 1	0.69	3.15E-04	-0.58	4.60E-04
SEMA4B	semaphorin 4B	0.76	7.28E-07	-2.37	9.35E-49
MT-RNR1	mitochondrially encoded 12S RNA	0.70	2.63E-08	-0.34	9.71E-03
SLC1A5	solute carrier family 1 member 5	0.27	2.60E-02	-1.33	3.61E-27
ESYT3	extended synaptotagmin 3	0.49	2.04E-02	-0.99	1.50E-05
FDFT1	farnesyl-diphosphate farnesyltransferase 1	0.38	1.04E-03	-0.40	1.32E-03
ENG	endoglin	0.27	2.77E-02	-1.22	2.40E-20
N4BP3	NEDD4 binding protein 3	0.38	3.14E-03	-0.61	3.99E-06
DDIT4	DNA damage inducible transcript 4	0.97	1.49E-09	-0.37	1.80E-02
FLVCR1	feline leukemia virus subgroup C cellular receptor 1	0.35	2.01E-03	-0.26	2.84E-02
RPL29P11	ribosomal protein L29 pseudogene 11	0.86	2.75E-02	-0.94	3.50E-03
TUBA1A	tubulin alpha 1a	0.43	9.53E-03	-0.80	4.59E-06
AC068888.1	uncharacterized LOC283335	0.51	4.51E-02	-0.98	7.88E-04
MT-ND5	mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 5	0.45	8.23E-04	-0.58	6.77E-06
ZNFX1	zinc finger NFX1-type containing 1	0.30	8.47E-03	-0.32	3.48E-03
SLC41A1	solute carrier family 41 member 1	0.35	2.20E-02	-0.81	1.16E-07
TMEM246	transmembrane protein 246	0.39	2.47E-02	-1.34	4.41E-11
CYP51A1	cytochrome P450 family 51 subfamily A member 1	0.43	5.13E-03	-0.67	8.13E-06
KCTD14	potassium channel tetramerization domain containing 14	1.36	4.89E-02	-2.30	3.21E-03
MKNK2	MAP kinase interacting serine/threonine kinase 2	0.37	1.07E-02	-1.61	5.98E-29
ENO2	enolase 2	0.41	2.00E-02	-0.55	1.04E-03
SNORA77	small nucleolar RNA, H/ACA box 77	1.88	4.32E-02	-3.10	9.98E-03
SH3TC1	SH3 domain and tetratricopeptide repeats 1	0.32	4.79E-02	-0.72	9.21E-05
C17orf49	chromosome 17 open reading frame 49	1.26	4.37E-02	-2.09	3.33E-03
AC012186.3	novel transcript	3.43	4.27E-02	-3.47	4.66E-02
GPRC5C	G protein-coupled receptor class C group 5 member C	0.48	9.74E-03	-1.02	2.53E-06
PCSK9	proprotein convertase subtilisin/kexin type 9	0.34	5.39E-03	-0.59	1.17E-05
ABHD17C	abhydrolase domain containing 17C	0.35	1.04E-02	-0.42	9.65E-03
PLEKHH3	pleckstrin homology, MyTH4 and FERM domain containing H3	0.44	6.92E-05	-0.28	4.83E-02
MT-TV	mitochondrially encoded tRNA valine	1.61	1.19E-03	-1.06	2.71E-02
SH3BP2	SH3 domain binding protein 2	0.39	8.43E-04	-0.49	1.77E-04
ST14	suppression of tumorigenicity 14	0.46	8.36E-03	-2.17	1.72E-32
MT-CYB	mitochondrially encoded cytochrome b	0.30	2.61E-02	-0.36	6.48E-03
PPP1R9B	protein phosphatase 1 regulatory subunit 9B	0.28	7.36E-03	-0.48	3.70E-05
EGLN3	egl-9 family hypoxia inducible factor 3	0.89	2.50E-02	-2.81	1.83E-07
DNAJB9	DnaJ heat shock protein family (Hsp40) member B9	0.48	2.09E-02	-0.44	3.76E-02
RARA	retinoic acid receptor alpha	0.36	2.49E-03	-0.51	6.14E-04
PTGS1	prostaglandin-endoperoxide synthase 1	0.37	2.94E-02	-0.45	1.09E-02
GRAMD1B	GRAM domain containing 1B	0.30	2.73E-02	-0.85	1.70E-10
HERPUD1	homocysteine inducible ER protein with ubiquitin like domain 1	0.60	9.10E-03	-0.80	2.04E-04

CDCP1	CUB domain containing protein 1	0.39	1.22E-03	-0.35	6.62E-03
PPFIA4	PTPRF interacting protein α 4	1.17	2.69E-02	-3.87	4.36E-06
SH2B3	SH2B adaptor protein 3	0.41	3.18E-03	-0.86	8.78E-08
AL117339.5	novel transcript	1.24	2.88E-02	-1.68	1.09E-02
ZNF385A	zinc finger protein 385A	0.27	3.29E-02	-1.23	2.69E-10
IL4R	interleukin 4 receptor	0.29	3.24E-02	-1.72	2.78E-30
LPAR5	lysophosphatidic acid receptor 5	0.54	2.43E-02	-2.50	4.02E-14
CNNM4	cyclin and CBS domain divalent metal cation transport mediator 4	0.39	2.44E-03	-0.40	6.32E-03
RN7SL431P	RNA, 7SL, cytoplasmic 431, pseudogene	1.54	2.92E-02	-2.35	7.24E-03
RCOR2	REST corepressor 2	0.58	4.37E-03	-1.47	2.62E-11
TNFRSF10D	TNF receptor superfamily member 10d	0.58	1.38E-02	-1.62	1.95E-12
TBC1D30	TBC1 domain family member 30	0.27	4.01E-02	-0.91	8.72E-10
ALDOA	aldolase, fructose-bisphosphate A	0.38	3.43E-02	-0.51	7.15E-03
HSPA5	heat shock protein family A (Hsp70) member 5	0.38	1.24E-02	-0.51	6.04E-04
AK4	adenylate kinase 4	0.40	1.92E-02	-1.70	4.94E-20
FAM214B	family with sequence similarity 214 member B	0.57	5.25E-03	-1.19	8.99E-06
MFSD2A	major facilitator superfamily domain containing 2A	0.56	2.26E-02	-1.88	7.51E-11
CHID1	chitinase domain containing 1	0.28	1.35E-02	-0.54	7.30E-05
DPYSL4	dihydropyrimidinase like 4	1.03	2.97E-02	-1.40	7.44E-03
AL513327.1	novel transcript	0.57	2.60E-02	-0.60	3.17E-02
HMOX1	heme oxygenase 1	0.62	5.90E-03	-0.77	3.76E-04
MICA	MHC class I polypeptide-related sequence A	0.41	1.36E-02	-0.65	3.75E-05
PPP1R3G	protein phosphatase 1 regulatory subunit 3G	1.25	1.37E-04	-3.16	3.00E-14
NSDHL	NAD(P) dependent steroid dehydrogenase-like	0.34	2.01E-02	-0.70	4.05E-06
TGFB1	transforming growth factor β 1	0.37	2.07E-03	-0.94	1.26E-11
PDIA5	protein disulfide isomerase family A member 5	0.34	2.47E-02	-1.90	1.22E-28
MIR210HG	MIR210 host gene	2.18	1.20E-05	-3.63	6.76E-09
AC122688.3	novel transcript	0.49	1.96E-02	-0.75	9.86E-04
AL049844.2	synaptophysin-like 1 (SYPL1) pseudogene	1.05	6.09E-04	-1.08	6.76E-04
MTND2P28	MT-ND2 pseudogene 28	0.34	2.11E-03	-0.57	7.09E-06
MT-ND1	mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 1	0.47	4.53E-04	-0.53	6.97E-05
LZTS2	leucine zipper tumor suppressor 2	0.28	4.36E-02	-2.09	9.71E-45
HEY1	hes related family bHLH transcription factor with YRPW motif 1	0.75	2.53E-06	-1.44	8.94E-16
MT-TH	mitochondrially encoded tRNA histidine	0.63	1.96E-03	-0.91	4.16E-05
FZD10	frizzled class receptor 10	0.64	5.77E-07	-0.35	1.03E-02
AL162274.1	novel transcript, antisense to BNIP3	1.62	1.86E-02	-2.31	5.98E-03
SQLE	squalene epoxidase	0.54	1.27E-04	-1.11	1.89E-14
MT-ATP8	mitochondrially encoded ATP synthase membrane subunit 8	0.31	2.62E-02	-0.56	7.84E-05
LPIN1	lipin 1	0.44	6.23E-03	-0.31	4.00E-02
ZMIZ1	zinc finger MIZ-type containing 1	0.35	9.95E-04	-0.75	2.88E-07

CREB3L3	cAMP responsive element binding protein 3 like 3	0.77	4.08E-02	-0.94	1.66E-02
C3orf58	chromosome 3 open reading frame 58	0.37	4.51E-03	-0.44	1.49E-03
PTPRB	protein tyrosine phosphatase, receptor type B	0.36	3.74E-02	-0.40	2.66E-02
ALDOC	aldolase, fructose-bisphosphate C	0.39	1.68E-02	-0.75	3.87E-06
MANF	mesencephalic astrocyte derived neurotrophic factor	0.47	2.30E-05	-0.29	1.89E-02

Supplementary Table 3. Summary of GO terms of PRGs and SRGs

GO terms	PRG		SRG	
	Gene Number	P.Value	Gene Number	P.Value
Biological Process				
adaptive thermogenesis (GO:1990845)	7	5.0E-06	3	4.5E-02
response to purine-containing compound (GO:0014074)	7	5.4E-06	1	5.5E-01
ossification (GO:0001503)	10	6.0E-06	2	5.9E-01
multicellular organismal homeostasis (GO:0048871)	11	7.6E-06	4	2.4E-01
response to steroid hormone (GO:0048545)	10	8.9E-06	5	5.4E-02
response to osmotic stress (GO:0006970)	5	2.4E-05	0	-
response to radiation (GO:0009314)	10	2.8E-05	2	6.8E-01
response to organophosphorus (GO:0046683)	6	3.7E-05	1	5.2E-01
tissue migration (GO:0090130)	8	4.0E-05	3	1.9E-01
pri-miRNA transcription by RNA polymerase II (GO:0061614)	4	5.0E-05	1	2.1E-01
nucleotide phosphorylation (GO:0046939)	0	-	6	1.1E-05
regulation of small molecule metabolic process (GO:0062012)	6	4.6E-03	10	1.2E-05
regulation of binding (GO:0051098)	4	8.4E-02	10	2.2E-05
cardiac chamber development (GO:0003205)	1	5.3E-01	7	2.5E-05
regulation of lipid metabolic process (GO:0019216)	6	7.5E-03	10	3.1E-05
pyruvate metabolic process (GO:0006090)	0	-	6	3.1E-05
nucleoside diphosphate metabolic process (GO:0009132)	0	-	6	3.5E-05
vasculogenesis (GO:0001570)	2	4.5E-02	5	4.6E-05
heart morphogenesis (GO:0003007)	5	5.4E-03	8	5.0E-05
regulation of DNA-templated transcription in response to stress (GO:0043620)	3	5.3E-03	5	5.6E-05
Cellular Component				
transcription factor complex (GO:0005667)	6	5.2E-03	2	5.9E-01
receptor complex (GO:0043235)	5	3.3E-02	7	6.0E-03
cell-substrate junction (GO:0030055)	5	3.8E-02	3	4.0E-01
midbody (GO:0030496)	3	4.3E-02	2	2.5E-01
transcriptional repressor complex (GO:0017053)	2	5.6E-02	1	3.8E-01
side of membrane (GO:0098552)	5	6.7E-02	4	2.8E-01
early endosome (GO:0005769)	4	6.8E-02	1	8.5E-01
nuclear chromatin (GO:0000790)	4	6.9E-02	4	1.2E-01
pigment granule (GO:0048770)	2	8.3E-02	2	1.2E-01
apical part of cell (GO:0045177)	4	9.1E-02	2	6.2E-01
outer membrane (GO:0019867)	1	6.1E-01	5	5.6E-03
ATPase complex (GO:1904949)	0	-	3	1.9E-02
endoplasmic reticulum lumen (GO:0005788)	2	4.1E-01	5	2.7E-02
basolateral plasma membrane (GO:0016323)	2	2.6E-01	4	3.2E-02
intrinsic component of endoplasmic reticulum membrane	2	1.6E-01	3	5.4E-02

(GO:0031227)				
myelin sheath (GO:0043209)	1	5.2E-01	3	5.7E-02
tertiary granule (GO:0070820)	0	-	3	6.2E-02
sarcoplasm (GO:0016528)	0	-	2	6.8E-02
extrinsic component of membrane (GO:0019898)	3	1.4E-01	4	7.5E-02
Molecular Function				
transcription corepressor activity (GO:0003714)	8	1.7E-05	4	5.1E-02
protein heterodimerization activity (GO:0046982)	9	4.0E-04	5	1.4E-01
SMAD binding (GO:0046332)	4	6.1E-04	0	-
DNA-binding transcription activator activity, RNA polymerase II-specific (GO:0001228)	8	1.3E-03	3	4.9E-01
protein kinase A binding (GO:0051018)	3	1.6E-03	1	2.5E-01
E-box binding (GO:0070888)	3	1.8E-03	0	-
cytokine receptor binding (GO:0005126)	6	2.1E-03	3	2.2E-01
enhancer binding (GO:0035326)	4	3.9E-03	0	-
growth factor receptor binding (GO:0070851)	4	3.9E-03	0	-
RNA polymerase II transcription factor binding (GO:0001085)	4	4.8E-03	4	4.8E-03
tetrapyrrole binding (GO:0046906)	2	1.5E-01	6	1.6E-04
oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen (GO:0016705)	1	5.4E-01	6	3.3E-04
cofactor binding (GO:0048037)	2	7.0E-01	9	2.4E-03
carbohydrate binding (GO:0030246)	0	-	6	4.7E-03
misfolded protein binding (GO:0051787)	0	-	2	6.8E-03
kinase regulator activity (GO:0019207)	2	2.6E-01	5	7.2E-03
Notch binding (GO:0005112)	0	-	2	7.4E-03
cofactor transmembrane transporter activity (GO:0051184)	0	-	2	7.4E-03
semaphorin receptor binding (GO:0030215)	0	-	2	8.1E-03
iron ion binding (GO:0005506)	1	5.2E-01	4	1.1E-02

Gene Number is the number of annotated PRGs or SRGs in the corresponding GO term.

Supplementary Table 4. Summary of KEGG terms of PRGs and SRGs

KEGG terms	PRG		SRG	
	Gene Number	P.Value	Gene Number	P.Value
Renal cell carcinoma (hsa05211)	5	3.8E-05	2	9.0E-02
Circadian rhythm (hsa04710)	3	6.7E-04	0	-
Rheumatoid arthritis (hsa05323)	4	1.6E-03	1	4.8E-01
Pathways in cancer (hsa05200)	9	2.1E-03	11	1.2E-03
HIF-1 signaling pathway (hsa04066)	4	2.3E-03	7	6.9E-06
Human T-cell leukemia virus 1 infection (hsa05166)	6	2.8E-03	2	5.6E-01
TNF signaling pathway (hsa04668)	4	3.3E-03	2	1.9E-01
Kaposi sarcoma-associated herpesvirus infection (hsa05167)	5	3.7E-03	1	7.5E-01
Proteoglycans in cancer (hsa05205)	5	4.8E-03	2	4.3E-01
Osteoclast differentiation (hsa04380)	4	5.6E-03	1	6.1E-01
Amphetamine addiction (hsa05031)	3	6.5E-03	2	8.8E-02
Terpenoid backbone biosynthesis (hsa00900)	2	6.7E-03	1	1.5E-01
Fluid shear stress and atherosclerosis (hsa05418)	4	7.3E-03	1	6.4E-01
Leishmaniasis (hsa05140)	3	8.2E-03	1	4.2E-01
Human cytomegalovirus infection (hsa05163)	5	8.2E-03	2	4.9E-01
Pertussis (hsa05133)	3	8.8E-03	1	4.3E-01
MicroRNAs in cancer (hsa05206)	4	9.7E-03	4	2.3E-02
Oxytocin signaling pathway (hsa04921)	4	1.0E-02	0	-
Colorectal cancer (hsa05210)	3	1.2E-02	1	4.7E-01
IL-17 signaling pathway (hsa04657)	3	1.5E-02	1	5.0E-01
Steroid biosynthesis (hsa00100)	0	-	6	2.8E-09
Glycolysis / Gluconeogenesis (hsa00010)	0	-	4	1.5E-03
Fructose and mannose metabolism (hsa00051)	0	-	3	1.7E-03
Carbon metabolism (hsa01200)	0	-	4	9.9E-03
Central carbon metabolism in cancer (hsa05230)	1	3.1E-01	3	1.2E-02
Biosynthesis of amino acids (hsa01230)	0	-	3	1.7E-02
Pentose phosphate pathway (hsa00030)	0	-	2	2.0E-02
Metabolic pathways (hsa01100)	3	9.9E-01	16	2.0E-02
Prion diseases (hsa05020)	1	1.8E-01	2	2.7E-02
Hepatocellular carcinoma (hsa05225)	1	6.2E-01	4	3.3E-02
Neomycin, kanamycin and gentamicin biosynthesis (hsa00524)	0	-	1	3.6E-02
Th17 cell differentiation (hsa04659)	2	2.2E-02	3	4.3E-02
Cocaine addiction (hsa05030)	1	2.4E-01	2	4.9E-02
Inflammatory bowel disease (IBD) (hsa05321)	1	3.1E-01	2	8.1E-02
Acute myeloid leukemia (hsa05221)	0	-	2	8.3E-02

Supplementary Fig. 1 Mn-regulated DEGs of A549 cells in the HIF-1 signaling pathway. The HIF-1 signaling pathway was downloaded from the KEGG database (https://www.kegg.jp/pathway/map04066). All genes involved in the pathway that were detected in the transcriptomic data are highlighted with a pink background. Within these regions, red font indicates primary response genes (PRGs), blue font denotes secondary response genes (SRGs), and black font represents other genes identified in the transcriptome.

