

Supplementary Methods:

Real-time quantitative reverse transcription-PCR (qRT-PCR)

Total RNA was isolated from treated cells with the Qiagen RNeasy kit (QIAGEN, Hilden, Germany), and 200 ng of total RNA was used to perform qRT-PCR using primers for Beta-ACTIN, ZNF423, RPL5, RPL7, RPL9, RPL15, RPS7 and RPS8 (Integrated DNA Technologies, Coralville, Iowa) with Power SYBR Green RT-PCR Reagents (Life Technologies, Carlsbad, CA). All experiments were performed in triplicate with beta-actin as an internal control.

Western blot and antibodies

Proteins from treated cells were extracted using NETN buffer (100 mM NaCl, 20 mM Tris-Cl (pH 8.0), 0.5 mM EDTA, and 0.5 % Nonidet P-40) with protease and phosphatase inhibitor cocktails (Roche, Basel, Switzerland). Antibodies against beta-actin (Sigma-Aldrich, St. Louis, MO), ZNF423 (Abcam, Cambridge, United Kingdom), AMPK, phospho-AMPK (Thr172), SIRT1, TAK1 (Cell signaling, Danvers, MA) were used to perform Western Blot analysis.

Label-free protein quantitative proteomic analysis

ZNF423 were knocked down by three individual ZNF423 siRNAs as three independent biological repeats. Proteins from treated cells were extracted using NETN buffer with protease and phosphatase inhibitor cocktails as describe above. Proteins were separated by SDS-PAGE and visualized by Coomassie Blue staining. Gels were excised into 12 pieces for each sample and were identified and quantitative by mass spectrometry (MS), performed by the Taplin Biological Mass Spectrometry Facility (Harvard Medical School, Boston, MA), as described previously [23]. Differential proteins were defined by average peptide ratios between the control and knockdown samples greater or less than 2-fold changes.

Cytotoxicity and colony formation assays

Cytotoxicity and colony formation assays were performed similar as previously described [16]. Briefly, CellTiter 96 AQueous Non-Radioactive Cell Proliferation Assays (Promega, Madison, WI) was used to detect the relative cellular viability in cytotoxicity assay. For colony formation assays, media and drugs were replenished every 3 days. After 14–28 days, cells were stained with crystal violet and the number of clones was counted. All experiments were performed in triplicate.

Supplemental Figure legends

Figure S1. Volcano plot for RNA-seq after knockdown of ZNF423 in ZR-75-1 breast cancer cells. Representative genes with the significantly changes were marked on the volcano plot.

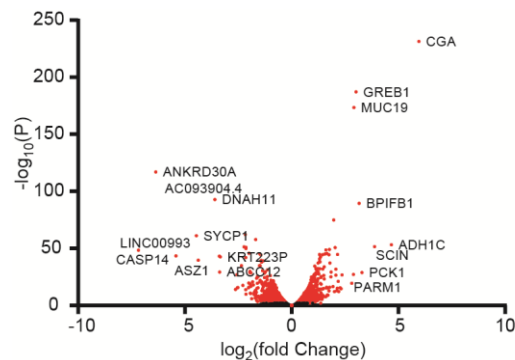


Figure S2. Real-time quantitative reverse transcription-PCR to validate the alterations of ribosomal protein genes modulated by the ZNF423 rs9940645 SNP, E2 and E2 plus tamoxifen. RPL5, RPL7, RPL9, RPL15, RPS7 and RPS8 were examined in ZR75-1 (V/V) and CRIS-ZR75-1(W/W) cells treated with E2 or E2 plus tamoxifen. The relative mRNA expression of these gene is shown as Mean $\pm$ SEM for 3 independent experiments.

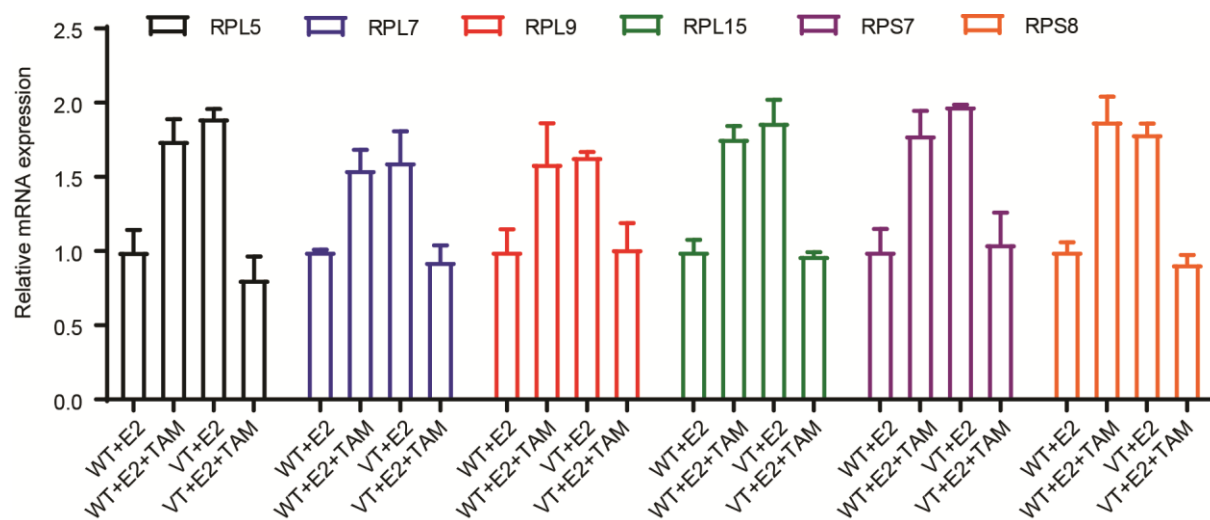


Table S1 RNAseq pathway analysis using the downregulated genes after ZNF423 knockdown

Term	Overlap	P-value	Genes
DNA replication	16/36	8.11×10 ⁹	RFC5;PCNA;RFC4;RFC1;RFC2;RPA2;POLA1;POLA2;POLE3;MCM3;MCM4;MCM5;MCM6;SSBP1;POLE;MCM2
Viral carcinogenesis	37/201	4.35 ×10 ⁻⁶	GTF2A1;HIST1H2BM;DDX3X;HIST1H2BO;HIST1H2BJ;YWHAB;HIST1H2BK;PIK3R3;PIK3R1;RBPJ;HIST2H4A;CASP8;CCND1;CASP3;CHEK1;HIST3H2BB;PRKACA;SKP2;PRKACB;RANBP1;JUN;SYK;ACTN1;GTF2H1;TRAF1;HIST2H2BF;NFKB1;CREB3;HIST1H4B;HNRNPK;RBL1;PKM;CCNE2;TRAF5;VDAC3;HIST1H2BF;HIST1H4I
Alcoholism	33/180	1.53 ×10 ⁻⁵	HIST1H2BM;SHC3;HIST1H2BO;HIST1H3J;HIST1H2BJ;HIST1H2BK;GNAI3;HIST2H2AC;HIST2H4A;PPP1CC;HIST1H3A;HIST3H2BB;PRKACA;HIST1H3C;HIST1H2AC;HIST1H2AB;HIST1H2AI;HIST1H2AH;H3F3A;H2AFV;HIST2H2BF;GRIN1;CREB3;HIST1H4B;HIST3H2A;HAT1;HIST1H2BF;GNB4;GNB3;HIST1H4I;CALM1;CALM2;SOS2
Spliceosome	27/134	1.55 ×10 ⁻⁵	RBM8A;EIF4A3;SRSF1;TRA2B;TRA2A;SNRPD3;SF3A3;HSPA8;PPIL1;NCBP1;ALYREF;CDC40;LSM3;HNRNPM;RBMXL1;HNRNPK;PRPF3;SNRPG;SRSF2;SRSF3;SNRPE;SNRPA1;SRSF6;RBMX;SRSF8;HSPA1B;HSPA1A
Mismatch repair	9/23	5.56 ×10 ⁻⁵	RFC5;PCNA;RFC4;RFC1;MSH2;RFC2;EXO1;RPA2;SSBP1
HIF-1 signaling pathway	20/100	2.10 ×10 ⁻⁴	EGLN1;EGLN3;TFRC;PIK3R3;ENO1;PIK3R1;ENO2;NFKB1;HK2;EGFR;VEGFA;LDHA;MKNK2;PGK1;AKT1;PLCG1;EIF4E2;ALDOA;GAPDH;PDK1
Systemic lupus erythematosus	24/133	2.71 ×10 ⁻⁴	HIST1H2BM;HIST1H2BO;HIST1H2AI;HIST1H3J;HIST1H2BJ;HIST1H2AH;ACTN1;H3F3A;HIST1H2BK;H2AFV;HIST2H2BF;HIST2H2AC;HIST2H4A;HIST1H3A;HIST1H4B;HIST3H2A;HIST1H2BF;HIST3H2BB;HIST1H4I;SNRPD3;FCGR1A;HIST1H3C;HIST1H2AC;HIST1H2AB
Insulin signaling pathway	24/137	4.27 ×10 ⁻⁴	SHC3;PRKAA2;PIK3R3;PIK3R1;HK2;CRKL;IKBKB;MAPK10;PPP1CC;PPP1R3C;PRKAR1B;PRKAR2B;RHEB;MKNK2;RAPGEF1;AKT1;INPP5K;PRKACA;CALM1;EIF4E2;PRKACB;CALM2;SOS2;SOCS4
p53 signaling pathway	15/72	8.02 ×10 ⁻⁴	CD82;THBS1;CASP8;TP53I3;CCND1;SESN3;CCNE2;AIFM2;ZMAT3;CASP3;CCNG2;CHEK1;FAS;CYCS;GTSE1
ABC transporters	11/45	9.83 ×10 ⁻⁴	ABCC3;ABCC4;ABCC2;ABCB10;ABCA5;ABCC5;ABCC6;ABCA12;ABCC11;ABCC12;CFTR

Table S2 Drug/SNP-dependent RNAseq pathway analysis (opposite SNP-drug dependent expression pattern of that of ZNF423)

Term	Overlap	P-value	Genes
Ribosome_Homo sapiens_hsa03010	17/137	4.52 ×10 ⁻²⁴	RPL4;RPL5;RPL3;RPS7;RPS8;RPLP0;RPL13A;RPSA;RPS3A;RPL9;MRPL24;RPL6;RPL7;MRPL30;RPL26;RPL15;RPS27A
Legionellosis_Homo sapiens_hsa05134	20/121	0.010399	EEF1A1;HSPD1
RNA transport_Homo sapiens_hsa03013	3/172	0.012414	EEF1A1;EIF3E;EIF4B
Carbon metabolism_Homo sapiens_hsa01200	2/113	0.03998	HADHA;ACO1
Proteoglycans in cancer_Homo sapiens_hsa05205	2/203	0.110694	EIF4B;ACTG1
Tight junction_Homo sapiens_hsa04530	2/139	0.057887	RAB13;ACTG1

Table S3 Drug/SNP-dependent RNAseq pathway analysis (same SNP-drug dependent expression pattern of that of ZNF423)

Term	Overlap	P-value	Genes
Influenza A_Homo sapiens_hsa05164	5/175	3.56 ×10 ⁻⁵	CXCL10;DDX58;TNFSF10;EIF2AK2;TNFRSF1A
RIG-I-like receptor signaling pathway_Homo sapiens_hsa04622	3/122	0.000458	CXCL10;DDX58;DHX58
TNF signaling pathway_Homo sapiens_hsa04668	3/110	0.001702	CXCL10;CCL20;TNFRSF1A
Cytokine-cytokine receptor interaction_Homo sapiens_hsa04060	4/265	0.002478	CXCL10;CCL20;TNFSF10;TNFRSF1A
Hepatitis C_Homo sapiens_hsa05160	3/133	0.002921	DDX58;EIF2AK2;TNFRSF1A
Sphingolipid signaling pathway_Homo sapiens_hsa04071	3/120	0.002182	ABCC1;GNA12;TNFRSF1A
Measles_Homo sapiens_hsa05162	3/136	0.003111	DDX58;TNFSF10;EIF2AK2
FoxO signaling pathway_Homo sapiens_hsa04068	3/133	0.002921	INSR;CCNG2;TNFSF10
Herpes simplex infection_Homo sapiens_hsa05168	3/185	0.007324	DDX58;EIF2AK2;TNFRSF1A
Regulation of actin cytoskeleton_Homo sapiens_hsa04810	3/214	0.010884	ENAH;ABI2;GNA12

Table S4 Proteomic pathway analysis using the upregulated proteins after ZNF423 knockdown

Term	Overlap	P-value	Genes
Ribosome biogenesis in eukaryotes_Homo sapiens_hsa03008	5/89	0.000298	RBM28;BMS1;RIOK2;GNL2;AK6
Purine metabolism_Homo sapiens_hsa00230	5/176	0.00609	POLE4;ENTPD2;POLR3A;AK6;HDDC3
Epstein-Barr virus infection_Homo sapiens_hsa05169	5/202	0.0107	POLR3A;TBPL2;TAB2;PTMA;MAP3K7
Herpes simplex infection_Homo sapiens_hsa05168	5/185	0.00748	IFIH1;OAS1;TBPL2;TAB2;MAP3K7
Measles_Homo sapiens_hsa05162	4/136	0.0123	IFIH1;OAS1;TAB2;MAP3K7
Vitamin digestion and absorption_Homo sapiens_hsa04977	2/24	0.0107	APOA1;SLC19A1
African trypanosomiasis_Homo sapiens_hsa05143	2/35	0.0220	APOA1;HBB
AMPK signaling pathway_Homo sapiens_hsa04152	3/124	0.0481	SCD;MAP3K7;SIRT1
Apoptosis_Homo sapiens_hsa04210	3/140	0.0644	TUBAL3;APAF1;KRAS
VEGF signaling pathway_Homo sapiens_hsa04370	2/61	0.0607	MAPKAPK3;KRAS

Table S5 Proteomic pathway analysis using the downregulated proteins after ZNF423 knockdown

Term	Overlap	P-value	Genes
Phosphatidylinositol signaling system_Homo sapiens_hsa04070	6/98	0.145	SYNJ1;INPP5J;ITPR1;PIK3CB;DGKZ;PIK3C2B
Metabolic pathways_Homo sapiens_hsa01100	24/1239	0.327	ALG9;GALT;AGPAT1;QRSL1;TYMS;ACACB;DGKZ;DHRS3;PIK3C2B;POLA2;MCEE;PTDSS1;SYNJ1;CHSY1;ADI1;NAPRT;KYNU;ATP5D;INPP5J;UPRT;MGAT1;SCLY;PNPLA2;POLR2L
T cell receptor signaling pathway_Homo sapiens_hsa04660	5/104	0.327	PPP3CC;CBLC;PIK3CB;MAP2K7;NCK1
Inositol phosphate metabolism_Homo sapiens_hsa00562	4/71	0.327	SYNJ1;INPP5J;PIK3CB;PIK3C2B
Glutamatergic synapse_Homo sapiens_hsa04724	5/114	0.327	ADCY9;PPP3CC;SLC1A1;ITPR1;SHANK2
ErbB signaling pathway_Homo sapiens_hsa04012	4/87	0.407	CBLC;PIK3CB;MAP2K7;NCK1
Apoptosis_Homo sapiens_hsa04210	5/140	0.407	ITPR1;XIAP;ATM;PIK3CB;FADD
Herpes simplex infection_Homo sapiens_hsa05168	6/185	0.407	PPP1CC;MED8;EIF2AK4;FADD;IFIT1;SRPK1
Inflammatory mediator regulation of TRP channels_Homo sapiens_hsa04750	4/98	0.407	PPP1CC;ADCY9;ITPR1;PIK3CB
mRNA surveillance pathway_Homo sapiens_hsa03015	4/91	0.407	PPP1CC;SMG1;NCBP2;PABPC1L2A