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Data Article

Data on the transcriptional response to MESH1 knockdown and mammalian stringent response

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ABSTRACT

MESH1 is the metazoan homolog of bacterial SpoT, the main phosphatase that dephosphorylates and degrades (p)ppGpp, the alarmone involved in the bacterial stringent response. The functional role of MESH1 in human cells is unknown. To define the global transcriptional response to MESH1 knockdown, we employed microarrays to perform transcriptome analysis of H1975 when the MESH1 was knocked down using three independent siRNAs targeting MESH1. The changes of each gene were derived by zero-transformation, followed by filtering to derive the genes affected by MESH1 knockdown. These datasets showed the transcriptional features of the mammalian stringent response and identified a prominent TAZ repression. Thus, we performed a second experiment to determine the contribution of TAZ repression to the transcriptional response of MESH1 knockdown by comparing the effects of MESH1-knockdown gene signatures in H1975 cells transduced with control or constitutive active TAZ (TAZS89A). The transcriptional response of these two cells to MESH1 was derived by zero transformation, followed by the effects of TAZ restoration to define the contribution of TAZ repression to the transcriptome features of human stringent response. The transcriptome data will be useful for the

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mechanistic understanding of the functional role of MESH1 in human cancer cells.

Specifications Table

Subject	Biological sciences Omics: Transcriptomic
Specific subject area	Study the function of human MESH1, a metazoan homolog of SpoT [1], a bacterial protein involved in regulating the level of (p)ppGpp and bacterial stringent responses. The transcriptional response to MESH1 shows significant similarity with the bacterial stringent response and potential evolutionary conservation [2].
Type of data	Table
How the data were acquired	In the first experiment, MESH1 was knocked down in H1975 cells by control or three MESH1-targeting siRNAs in triplicates [3,4]. Total RNAs were collected, and their quality was assessed with the Agilent BioAnalyzer. 200 ng RNA was used to generate cDNA using the Ambion MessageAmp kit and interrogated with an Affymetrix U133A GeneChip. The microarray data was normalized by the RMA, and zero transformed to the negative control (siNT) as before [5,6]. The transcriptional responses to MESH1 knockdown (Table 1) are based on the filtering criteria of at least seven observations with absolute log2 values >0.47. GSEA (Gene Set Enrichment Analysis) revealed a depletion of multiple cell cycle and proliferated pathways upon MESH1 knockdown. MESH1 knockdown also reduced the expression of RRM1 (ribonucleotide reductase M1) and RRM2, subunits of ribonucleotide reductase (RNR) responsible for dNTP synthesis. In the second experiment, the contribution of TAZ repression to the transcriptome response was defined by comparing MESH1-knockdown gene signatures between the control and TAZS89A-transfected H1975. TAZ restoration reversed the changes of at least 1.5 fold of the MESH1-affected genes (Table 2).
Data format	Analyzed Filtered
Description of data collection	Total RNAs were isolated by RNeasy Mini Kit (Qiagen, #74104) and used to generate cDNA using the Ambion MessageAmp Premier RNA Amplification. The labeled cDNA samples were interrogated with an Affymetrix U133A GeneChip. The data were normalized by the RMA and the expression value of each genes in the siMESH1 groups was compared with the expression value of the same genes in the negative control (siNT) to derive the changes in gene expression. Data were then filtered with Cluster 3.0 and clustered by the genes and shown in tables.
Data source location	• Duke School of Medicine • Durham, North Carolina • USA
Data accessibility	Name: NCBI Gene Expression Omnibus https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE135358 The transcriptional response to MESH1 silencing https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE135346 TAZ overexpression partially rescued the transcriptomic reprogramming triggered by MESH1 silencing Mendeley Data: Chi, Jen-Tsan Ashley (2022), "Genes whose expression are affected by MESH1 knockdown in H1975", Mendeley Data, V2, doi:10.17632/hgy8rxmj62.2
Related research article	For a published article: Sun T, Ding CC, Zhang Y, Zhang Y, Lin CC, Wu J, Setayeshpour Y, Coggins S, Shepard C, Macias E, Kim B, Zhou P, Gordân R, Chi JT. MESH1 knockdown triggers proliferation arrest through TAZ repression. Cell Death Dis. 2022 Mar 10;13(3):221. doi:10.1038/s41419-022-04663-6. PMID: 35273140; PMCID: PMC8913805.

Value of the Data

- These data are the first transcriptome studies of the functional role of MESH1 in human cancer cells.
- Transcriptome analysis of mammalian stringent response will enable the cross-kingdom analysis from bacteria [7], Drosophila [1] and human cancer cells [3,4,8].
- Ferroptosis is a newly recognized form of cell death with important disease relevance [9]. We have performed forward genetic screens to identified many novel determinants of ferroptosis [10–13]. MESH1 was identified in a genome-wide RNAi screen [14] and the knockdown of MESH1 robustly protected ferroptosis [4]. In addition, MESH1 knockdown is associated with dramatic proliferation arrest with therapeutic potential. Therefore, the data presented may provide insight into ferroptosis.
- The data could be of interest to any investigators interested in the bacterial stringent response and other stress responses in different organisms across evolution.
- These data represent a novel stress response of human tumors that has not been described.
- The transcriptome data can be useful for another investigator to study the conservation of stress response.
- Identify the unexpected association between other biological processes and chemical/genetic perturbations.

1. Objective

While MESH1 was found to regulate ferroptosis by degrading NADPH, its knockdown also robustly reduced the proliferation of cancer cells. To understand the mechanisms underlying such dramatic phenotypes, we performed transcriptome analysis to fully characterize the genes and molecular pathways affected by MESH1 knockdown. Such analysis will also allow us to compare the transcriptional response of mammalian stringent response with what has been published in flies and bacteria. These data highlighted the importance of TAZ mRNA repression as a critical feature of the MESH1 knockdown and mammalian stringent response. Therefore, we performed the second transcriptome experiment in which TAZ is over-expressed as MESH1 was knockdown. These experiments allowed us to dissect the transcriptome changes of MESH1 knockdown into TAZ-dependent vs. TAZ-independent components. The data article adds value to the published articles by highlighting the scientific rationales and experimental designs of these two transcriptome experiments for the academic community.

2. Data Description

To define the transcriptional response to MESH1 knockdown, we knockdown MESH1 in H1975 cells with independent siRNAs and performed transcriptomic analysis [2].

First, the raw data in the GSE135358 were generated by the microarray interrogation of the RNA samples of H1975 transfected with control or three different siRNA targeting MESH1 in triplicate [3,4]. After 48 h of transfection, the total RNAs were collected from these cells and quality was validated using the Agilent BioAnalyzer. 200 ng RNA was used to generate cDNA using the Ambion MessageAmp kit and interrogated with an Affymetrix U133A GeneChip. The microarray data were normalized by the RMA, and zero transformed to the negative control (siNT) as before [5,6].

Table 1 showed the genes whose expression was affected by MESH1 knockdown in H1975 cells. The microarray data were normalized by the RMA, and zero transformed to the negative control (siNT) as before [5,6]. The genes were then filtered based on the filtering criteria of at least seven observations with absolute log2 values >0.47 and cluster of genes affected by MESH1 knockdown were listed in Table 1. The seven was used as filtering criteria to select changes

Table 1
List of differentially expressed genes in H1975 upon the knockdown of MESH1 by three independent siRNAs targeting MESH1.

Gene Symbol
NREP
NREP
HDAC5
SYT1
CA11
AKR1C3
PCDHA1 /// PCDHA10 /// PCDHA11 /// PCDHA12 /// PCDHA13 /// PCDHA2 /// PCDHA3 /// PCDHA4 /// PCDHA5 /// PCDHA6 /// PCDHA7 /// PCDHA8 /// PCDHA9 /// PCDHAC1 /// PCDHAC2
ZNF467
KLRC3
GSN
ARG2
DDAH1
NMNAT2
CDC14B
DIP2C
DZANK1
RUNDC3A
STK19
HIST1H2BC /// HIST1H2BE /// HIST1H2BF /// HIST1H2BG /// HIST1H2BI
HIST1H2BE
HIST1H2BD
HIST1H2BC /// HIST1H2BE /// HIST1H2BF /// HIST1H2BG /// HIST1H2BI
IFT22
INPP5A
SIK1
CFB
ATF3
RHOD
KLK6
MGLL
UAP1L1
DSP
KLHDC3
KLHDC3
GOLGB1
DDAH2
DDAH2
DDAH2
TPM4
KDM2A
CCDC176
FLRT2 /// LOC100506718
CCPG1 /// DYX1C1-CCPG1
CCPG1 /// DYX1C1-CCPG1
RRAGD
LCAT
ZBTB5
CFDP1
IQCJ-SCHIP1 /// SCHIP1
SAT1
SAT1
SAT1
CASP7
UBE2L6
RABAC1
OAZ3
C11orf80
NABP1

(*continued on next page*)

Table 1 (*continued*)

Gene Symbol
ITGB5
PLAG1
CXADR
COL18A1
PIM1
MCCC1
OPTN
VAMP5
ATP9A
HABP4
ZER1
CDC14B
HBP1
TBC1D9
UBAP2L
AKR1A1
BBS1
CTSB
E2F3
EHD1
EHD1
EHD1
DNAJC1
ARID3A
CCDC93
CARS
RRAGD
TMEM43
DYNC1H1
TTC9
CARHSP1
SIGIRR
SIGIRR
SPCS3
LPIN2
LTBP1
ITGB5
HDAC9
C11orf95
ADCY9
SLC2A3
DNAJB9
CTSB
SLC2A3
CTSB
EDEM1
SLC2A14 /// SLC2A3
KLF9
AGR2
ZNF83
G3BP2
ZNF267
PHACTR2
ACYP2 /// LOC101927144
PAEP
VPS28
CREBL2
DLG5
ANKRA2
KIAA1598
02-Mar

(*continued on next page*)

Table 1 (*continued*)

Gene Symbol
HIST1H1C
CDKN1C
CDKN1C
—
CDKN1C
CDKN1C
AHNAK2
CREBL2
IFT20
FOS
KDR
KCNJ15
DPYSL3
MTF2
RSL1D1
PHTF2
RSL1D1
HIST1H2BC /// HIST1H2BE /// HIST1H2BF /// HIST1H2BG /// HIST1H2BI
ANGPTL4
IL24
OSTM1
MAFF
DUSP3
PHACTR2
RGL2
STX4
SPAG7
TUSC3
CTSB
CDYL
NUPL1
BIK
EFTUD1
RAB17
PLEKHA1
KAT2B
ZNF702P
LY96
CHIC2
MAPK6
TLK2
CBY1
EMC6
CDC37L1
IL6R
CREB3
ARL14
MUT
JUN
HIST1H4H
IFT88
HIST1H2AG /// HIST1H2AH /// HIST1H2AI /// HIST1H2AK /// HIST1H2AL /// HIST1H2AM
BSPRY
HIST1H2BG /// HIST1H2BJ
HIST1H2AE
BICD2
HIST2H2AA3 /// HIST2H2AA4
HIST2H2AA3 /// HIST2H2AA4
LINC00339
S100A13

(*continued on next page*)

Table 1 (*continued*)

Gene Symbol
PSENEN
CCDC53
AHNAK
DDX43
C2orf54
MAD2L1
CCT2
MCM6
PLK1
GTSE1 /// TRMU
EPB41L2
ACOX2
ACLY
ABCE1
EVI2B
SRSF1
LHX6
ACLY
EOGT
PRPS1
KIF14
MIR636 /// SRSF2
RAD54B
RFWD3
MDFIC
NAA50
MIS18BP1
SLC29A1
STRAP
MRTO4
TMPO
RAC2
HNRNPH1
H2AFX
IL1RL1
TUBGCP3
UBE2D2
ARHGAP22
RAB28
KPNA4
PARN
DUSP9
TLE3
FBXO11
NBN
HIP1
RGS4
GJA9-MYCBP /// MYCBP
HNRNPA2B1
DAZAP1
ARTN
ARTN
ARTN
PPP6R3
RBM8A
NHLRC2
WDR77
WWTR1
PRR3
IDH3A
PRPF4

(*continued on next page*)

Table 1 (*continued*)

Gene Symbol
NAA15
ARF6
HIPK2
IL1RN
C6orf62
STIP1
BCLAF1
BCLAF1
NBN
WWTR1
PIGL
DHX15
SERBP1
MIR4745 /// PTBP1
SMC4
GPR107
BUB1
ENO1
PRKAR2B
CD44
LOC101928747 /// RBMX /// SNORD61
DARS2
CEP152
SRSF11
BCLAF1
TRIM14
TRIM14
MBNL1
TMED2
ARF1 /// MIR3620
TUBB2A /// TUBB2B
STC1
STC1
CSNK2A1
LPAR1
RBM12
ZNF586
HNRNPD
SORD
SORD
BASP1
PDHA1
HNRNPD
06-Mar
KIAA1462
PRMT3
NT5DC2
PTGES
C6orf62
PRKX
TIA1
H2AFV
H2AFV
FAM115A /// LOC100294033
FAM115A /// LOC100294033
ELAVL1
ALDH3A2
ALDH1A3
KRAS
ARMC9
ZNF207

(*continued on next page*)

Table 1 (*continued*)

Gene Symbol
GPR125
ADO
CYB5B
DESI1
LIPG
GTPBP8
SDHD
LRRC59
MRPL44
GPRC5B
SCLY
FUBP1
ANKLE2
QRSL1
AMACR /// C1QTNF3-AMACR
SPATS2L
MALL
PSME3
HNRNPUL1
NAP1L1
OPA1
PPP2R1B
TRIM14
LRRK1
ACTR3B
HNRNPUL1
MAP3K7
ACSL3
ACSL3
SEC23IP
ARHGEF26
ALDOC
METAP1
POT1
FASTKD2
PUS7
GATC
IL18
CALML4
CALML4
TIA1
NAP1L1
RRP15
PEG10
CA2
ARHGAP29
ACTB
FCF1
ABLIM1
THEMIS2
U2SURP
PAPOLA
HHEX
METAP2
PTER
DLG1
TAF6L
FAH
EVI2A
NETO2
CDK1

(*continued on next page*)

Table 1 (*continued*)

Gene Symbol
CDC25C
CDC6
SRSF6
GINS1
FADS1 /// MIR1908
FADS1 /// MIR1908
FADS1 /// MIR1908
CBLL1
NRP1
DKK1
VDAC1
FUS
TBCE
CKB
AASDHPPT
HIRA
ATP2A2
STARD7
WDR3
MOCOS
LRRC40
GEMIN2
AIDA
RRM2
RRM1
RRM1

consistent in more than two sample groups. Such analysis revealed a prominent transcriptional repression of TAZ, but not YAP, upon MESH1 knockdown.

Next, to determine the role of TAZ repression in the transcriptional response of MESH1, we produced the raw data in GSE135346. H1975 cells were first transduced by control empty vector or TAZS89A, a constitutive form of TAZ. The cells were then selected by puromycin to select cells with control or TAZS89A-overexpression lentivirus. These cells were then transfected with control or MESH1-targeting siRNAs for 48 h. At this point, the total RNAs were collected from these cells and quality was validated using the Agilent BioAnalyzer. 200 ng RNA was used to generate cDNA using the Ambion MessageAmp kit and interrogated with an Affymetrix U133A GeneChip. The microarray data were normalized by the RMA, and zero transformed to the negative control (siNT). Table 2 showed the list of genes whose expression was affected by MESH1 knockdown, but then reversed upon TAZS89A expression by at least 1.5-fold (Table 2).

Table 2
List of differentially expressed genes affected by TAZS89A at least 1.5-fold in MESH1-knockdown H1975.

Gene Symbol
BLNK
AKR1C3
CCL5
HOXD1
KIAA0125
VTCN1
CCL5
CHI3L1
CHI3L1
PDE4DIP /// LOC727893
TNFSF10
CLIC2
SP100
C5orf13
MN1
C10orf81
CLEC2B /// CDRT15P
HLA-DPA1
NFE2
HLA-DRA
NAV3
SOX2
ABCA1
POU2F3
LYPD1
SPP1
VAV3
GNAL
GBP1
CTSS
PDE4DIP
ABCA1
GBP1
ZBTB1
HLA-DMB
HLA-DRA
TNFSF10
HLA-DMA
MSMB
BIRC4BP
PDE4DIP
NAV2
LMO2
TJP3
CASC1
C9orf61
HPGD
TJP3
CTSS
OAS1
GBP2
MMP13
ABCA12
AGT
MPPE1
CYR61
KLHL24
TNFSF10
INDO
CYR61

(*continued on next page*)

Table 2 (*continued*)

Gene Symbol
SNAI2
BDKRB2
PDGFD
KLRC3
FA2H
GRAMD1C
HPGD
S100P
MUC16
CMAH
TP73L
SLC28A3
IGHA1
MX1
04-Sep
CFB
MAF
LDB3
HPGD
MPPE1
KLHL24
OAS1
IL1R1
AVIL
RSAD2
ABAT
CEBPD
IGHA1 /// IGHA2
RALGPS1
SLC16A4
ADRB1
CTNNA2
SLAMF7
KLF4
ASAH1
PDE4DIP
VPS13C
GABARAPL1 /// GABARAPL3
KLF4
CTGF
RAB15
DSC2
C5orf13
HIST1H4H
ISGF3G
HIST1H2AM
HIST1H2AE
MGC17330
MLLT3
TncRNA
HERC6
PBXIP1
HIST1H2AG
LOC653483
—
SLC2A5
SLC12A8
KLF2
C5orf13
MIA3
STK38L

(*continued on next page*)

Table 2 (*continued*)

Gene Symbol
LASS4
TXNIP
NUPR1
HDAC9
GABARAPL1
PBXIP1
ASAH1
IFI44L
GLUL
FGFR3
—
RELN
CDH5
PPAP2A

3. Experimental Design, Materials and Methods

The primary objective of this experiment was to identify the genes whose expression might be affected by the knockdown of the MESH1 as the transcriptional features of the mammalian stringent response. Furthermore, we will determine the degree to which TAZ restoration can mitigate the transcriptional response to the MESH1 knockdown.

3.1. Cell Lines and Cell Culture

H1975 cell lines were obtained from ATCC and cultured in the standard cell culture conditions with DMEM with 10% FCS, glutamine and penicillin/streptomycin. To mimic the loss of MESH1, we transfected H1975 with control siRNAs and three additional siRNAs that target MESH1 at different regions of MESH1 mRNA. The successful knockdown of the MESH1 were validated by qRT-PCR and Western blots.

3.2. RNA Extraction, Quality Control and Microarray Profiling

Total RNA was extracted from H1975 cells treated with control of MESH1-targeting siRNAs in triplicate using RNeasy Mini Kit (Qiagen, Germany) based on the manufacturer's protocol. Total RNAs were collected with RNeasy Mini Kit (Qiagen, #74104) and assessed with the Agilent BioAnalyzer. RNA quality and quantity were determined using Bioanalyzer (Agilent Corporation, USA) and NanoDrop spectrophotometer (Thermo Fisher Scientific, Wilmington, USA) for concentration cDNAs were generated from 200 ng RNA using the Ambion MessageAmp Premier RNA Amplification (Life Technologies, Grand Island NY, USA) to generate biotin-labeled samples for hybridization. The resulting probes were then hybridized with GeneChip arrays overnight in the Affymetrix hybridization oven at 42 °C. Next, the Affymetrix GeneChip Fluidics Station 450 performs the automated Affymetrix wash and stain protocols. Afterward, The Affymetrix GeneChip Scanner 3000 7G is used to generate the resultant GeneChip array image at the Duke Microarray Facility.

3.3. Data Analysis

The microarray data were normalized by the RMA (Robust Multi-Array) algorithm. and zero transformed to the negative control (siNT), where we compared transcript levels for each gene

in siMESH1 groups to the siNT group ($n = 3$ biologically independent replicates in each siRNA group). Data were then filtered with Cluster 3.0 based on the criteria at least seven observations with absolute log2 values >0.47and then clustered by the genes. The list of genes affected by MESH1 knockdown were shown in Table 1. For the TAZ-affected genes, the genes were selected by affecting at least 1.5-fold by TAZS89A as shown in Table 2.

Ethics Statements

This study does not involve human subjects or samples derived from human materials. It also does not involve vertebrate animals. However, we have used human cancer cell lines from ATCC and other commercial sources, whose use has been approved under the Duke Biosafety Protocol 14-0048-05.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The transcriptional response to MESH1 silencing (Original data) (GEO).
TAZ overexpression partially rescued the transcriptomic reprogramming triggered by MESH1 silencing (Original data) (GEO).

CRediT Author Statement

Tianai Sun: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing; **Chien-Kuang Cornelia Ding:** Conceptualization, Methodology, Investigation, Writing – review & editing; **Jen-Tsan Chi:** Conceptualization, Supervision, Project administration, Funding acquisition, Writing – review & editing.

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