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Supplemental Methods:

Genome-Scale Gene-Expression High Throughput Screening

Precautions: Since RNA oligonucleotides are susceptible to degradation by RNAses and non-specific degradation, they were handled and stored using RNAse-free conditions and reagents.

Background: The majority of the procedure is based on Dharmacon's Wet Reverse Transfection Version 2.0 protocol with modifications developed for use with the equipment and layout of the siRNA Screening Facility. The following procedure describes a high-throughput siRNA screen in HCT116 (Human Colon Tumor) cells. Screening plates were performed in triplicate. Therefore, each 384-well "screening" library plate (1 μM) was used to generate three replicate daughter experimental screening plates. For each screening session, eight library plates (samples) were placed into process resulting in a total of 24 transfected 384-well plates. This number of plates maintained the temporal (72 hours) parameters and considerations of the screening experiment and complex gene expression endpoint assay. It was well within the HTS capabilities of the automated platform to perform more than one screening session per day and/or per week. In this sample protocol, the upper-limit of HTS capacity was being controlled by the endpoint "Quantigene 2.0 assay- Panomics", which only requires that the samples be properly lysed over the course of 90 minutes, and frozen at -80°C. Frozen samples were stable for a period of at least 18 months and were thawed once before being assayed. This allowed the workflow to be separated into two parts: 1) the transfection (using a 384 well head for the Biomex FX) and lysis (using a 96 well head for the Biomex FX) and 2) Quantigene 2.0 assay from Panomics (using a 96 well head for the Biomex FX).

The Generation of Samples

Preparation

Each liter of propagation medium was prepared by adding 125 ml FBS (serum Lot M0017 from Atlanta Biologicals), 12.5 ml L-GlutaMax and 12.5 ml of Non-Essential Amino Acids to 850 ml of 1X DMEM from Cellgro. Final total volume was 1 L (12.5% FBS, L-Glutamine, and NEAA). Prepared medium was generated the day before, filtered through a 0.22 micron membrane into a sterile plastic container and was stored at 4°C overnight. Note: Propagation medium is made without antibiotics as they interfere with the optimal uptake of siRNA in a lipid-mediated transfection protocol. Four to five days before transfection, one ml vial of cells were thawed into 10ml of fresh media and containing fresh 10% FBS culture media with antibiotics, and plated into a 10-cm dish. All plates were placed at 37°C in a 5% CO2 incubator. The following morning, all culture flasks were re-fed with 10 ml of fresh propagation medium to remove any traces of DMSO from the freezing medium and cultured for two passages at 37°C in a 5% CO2 incubator. For screening sessions, three million cells were plated on a 10-cm culture dish and allowed to grow for 48 hours before transfection. 2-3 dishes were required to complete large transfections. Each dish contained roughly 10 million cells. 1X Hank's Buffered Saline Solution

(HBSS) was prepared by adding 9.8 g of HBSS powder to 1 liter of Sigma HPLC-purified, sterile, RNAse-free, deionized water and filtered through a 0.22 μm filter. No sodium bicarbonate was added. Eight sets of 3 Nunc 384-well flat-bottom microtiter tissue culture plates (#164688) were barcode-labeled with proper identifiers for future tracking. In addition, eight BioRad 384-well polypropylene conical bottom PCR plates (cat #MSP3842) were labeled with proper plate identifiers (1 plate/master screening plate). All work surfaces were cleaned with a detergent cleanser and sterilized with 70% ethanol.

Transfection (Day 0)

This protocol was optimized for use with HCT116 cells in 384-well format. The final concentration of SMARTpool siRNA is ~50 nM; the final transfection volume was 30 μl; there were 2,500 cells per well; the volume of Dharmafect 4 was 0.05 μl/well. Eight master library plates (384-well format) were evaluated for each transfection session. Plates were removed from -20°C and allowed to warm to room temperature. Plates were subsequently centrifuged in a Sorvall RC7 tabletop centrifuge (1000 rpm x 3 minutes). In a BCS hood, the Dharmafect 4/HBSS reagent was prepared to provide enough reagent for 24 x 384 well final screening plates with extra volume for dilutions, pipetting and a Microdrop void volume of 3 ml. [Calculations to assure enough working volume were made based on the following conservative estimates and assumptions: Eight master assay plates generated three daughter replicate screening plates multiplied by 400 wells (8 master plates x 400 wells/plate = 3,200 wells). Each well needed 15 μl DF4/HBSS before the addition of siRNA (3,200 wells x 15 μl/well = 48,000 μl of DF4/HBSS). In addition, 3ml of HBSS/DF4 was required for priming and void volume in the microdrop dispenser (48ml + 3 ml = 51 ml). Since the ratio of HBSS/DF4 needed to be 106:1 prior to the 33% volume addition of siRNA for complexing (see below), ~566 μl of DF4 was added to 60.0 ml of HBSS. (60,000 μl / 106 ul of HBSS/ μl DF4 = 566 μl Dharmfect 4 into 60 ml of HBSS]. Using a Microdrop dispenser fitted with 11 mm stage (Thermo-Fisher), 15 μl of DF4/HBSS reagent was added to each well of eight empty master assay screening plates. Foil adhesive seals were removed from each siRNA containing master screening plate in a BSC hood. Using the Biomek F/X with 384-well tip head, 5 μl of the 1 μM siRNA solution from the master library plate was added to the 15 μl DF4/HBSS mix in its corresponding 384-well master assay screening plate and mixed four times (12 μl aspiration volume). After completion of the transfer, the master assay screening plate was centrifuged (1000 rpm x 3 minutes) in a Sorvall RT7 tabletop centrifuge and subsequently allowed to set at room temperature. Simultaneously, the 384-well master library plate was resealed with ABgene PCR heat foil seal and stored in a -80°C freezer. Triplicate assay screening plates were created with the Biomek F/X (384-well tip head) by transferring 6μl of the siRNA/DF4/HBSS complex from the master assay screening plate to three 384-well Nunc flat-bottom tissue culture screening plates. As the screening plates were being dispensed, cells were simultaneously processed to yield 100,000 cells/ml. Each 384 well plate required 10 ml of cells at the desired concentration. A typical 10 cm dish yielded at least 10,000,000 cells in 10 ml of media. Therefore, one 10-cm dish was approximately enough cells

for 15 384-well screening plates. Therefore, to be safe, three 10-cm plates were processed to ensure enough cells for 24 plates. Medium was removed from 3 10-cm dishes and adherent cells washed one time with 5 ml of 1X PBS per dish. Cells were then washed again in 5 ml of 1X PBS with 5 mM EDTA. After 1 minute, the PBS/EDTA solution was removed. Each plate of cells received 1 ml of 1X trypsin per dish and was incubated 5 minutes at 37 ºC. Cells were fully detached at this point. Trypsin was neutralized by adding 12 ml of transfection medium to each dish and the cells were resuspended into a solution of single cells by pipetting up and down. Cells were then passed through a 40 µM screen into a 50ml Sarstedt conical tube to eliminate clumping. Resuspended cells from each dish were combined, mixed, and counted by hemocytometer. The cell suspension was diluted with transfection medium to a final concentration of 100,000 cells/ml in a fresh, sterile, plastic 1L Erlenmeyer flask and mixed evenly by gently pipetting and swirling. Using Multidrop dispenser with 15 mm stage, 25 µl of cell suspension/transfection medium were added to each well of each set of three 384-well transfection plates. Final volume in each well was 31 µl. Cells were NOT centrifuged before being placed at 37°C in a 5% CO2 incubator. At 72-hours after transfection cells were lysed using the 96-well head on the BiomexFX. 20 µl of lysis buffer (containing 10 µl of Proteinase K per ml lysis buffer) was added to each sample. The sample was mixed 40 times using 28 µl mixes. The lids were replaced on each plate and placed into a 37°C incubator. After 60 minutes at 37°C, each plate was mixed an additional 20 times, sealed at 175°C for 4 seconds, and frozen at -80°C until assayed. Natural Product Screen: 2.0×10^4 HCT116 cells were plated in 50 µl of normal culture medium in 384-well tissue culture plates. After 48 hours post plating, cells were treated with 60 µg/ml of natural product extract (0.3 µl) or indicated concentration of known drug for 21 hours. Cells were lysed and gene expression signatures were determined.

Gene Expression Determination through Branched DNA Signal Amplification (Quantigene2.0 reagent system – Panomics/Affymetrix)

Day 0

The day before cell lysis, set heat block to 95°C, set waterbath to 42°C, and set Cytomat 2 to an internal temperature of 54°C.

Day 1

The following protocol is based on the processing of two 384-well screening plates that have been lysed (~50 µl/well) and stored at -80°C.

General Notes

The protocol is based on the use of eight fluorescent magnetic bead panels with each bead panel comprised of eight different fluorescent magnetic beads (Total number of individual fluorescent bead classifications=64). One bead panel will be used for the equivalent of a 96-well plate (1/8 of two different 384-well lysate plates or 1 96-well quadrant per 384-well sample plate). Each

bead panel is made up in a separate bead/reagent master mix (detailed below) at a sufficient volume (30 µl/well) for the equivalent of 110 wells. Each bead panel will be added to the appropriate quadrant of a Greiner 384-well polypropylene plate (cat/ref# 781201). Cell lysate (40 µl) is added directly to the bead/reagent mix of each individual well. Total final volume of the bead/reagent/lysate hybridization mix is 70 µl. The wells of both Column 1 and Column 24 are suctioned dry, and then receive 40 µl of HPLC-water. (Note: prior to lysate transfer Column 1 and Column 24 of each sample plate contain lysis buffer as part of the original screening plate lysates. However, these wells do not contain any siRNA samples.

Preparation of 1X Solutions:
Notes: All solutions are prepared on the day of the experiment and can be scaled accordingly.

To begin, remove lysate screening plates from -80°C freezer and place in refrigerator. Fill ice bucket. Warm the lysis buffer (stored at RT) in 42°C water bath in order to dissolve all buffer components. Add 10 µL of Proteinase K to each ml of lysis mixture. To prepare 200 ml wash buffer, add 10 ml of wash buffer component 2 and 0.6 ml of wash buffer component 1 into 190 ml of MilliQ water. To generate the preamplifier solution, warm up label probe diluent at 37°C for 30 min. Add 54 µl of preamplifier to every 1ml of label probe diluent. To generate the amplifier solution, warm up label probe diluent at 37°C for 30 min. Add 54 µl of Amplifier to every 1ml of label probe diluent. To generate the label probe solution, warm up label probe diluent at 37°C for 30 min. Add 54 µl of Label Probe to every 1ml of Label Probe diluent. To generate the SAPE solution, add 7.5 µl of SAPE to every 1ml of SAPE diluent.

Master Mix Setup
Amount per well
- Lysis mixture 10 µl
- Proteinase K 0.2 µl
- Blocking reagent 2.0 µl
- Probe mix 5.0 µl (Heat at 95°C for 5 min to denature – then put on ice)
- Bead mix 1.0 µl (Vortex well, Do NOT sonicate)
- Water 11.8 µl
- TOTAL 30 µl

(40 µl of lysate + 30 µl of master mix = 70 µl)

Probe Preparation:
Probe Set = Plex Set 11185, Human, 8 x 8
A total of 4,400 µl of heat-denatured probe was used for the current protocol. Thaw the probe (stored at -20°C). Aliquot 1 ml into five sterile 1.5 ml microcentrifuge tubes. Ensure cap

clips/holders are on each tube and place all five tubes in 95°C heat block for 5 min. Remove and immediately place tubes on ice. (Unused probe can be frozen and reused in future hybridizations.) Each tube panel should be made up in sterile 15 ml centrifuge tubes. Reagents for each tube panel are added in the following order and volumes: Emphasis-This is for the equivalent of 110 lysate wells. Adjustments need to be made if a larger multiple of lysate plates are being processed. Move lysate plates from 4°C to 37°C incubator. Plates take on average 30 minutes to thaw and will change from pink to yellow when thawed. Add the following to each well:

1. HPLC-water (1300 µl) -- use a P1000 pipette to add 2x aliquots of 650 µl each.
2. Lysis buffer (1100 µl) – use a P1000 pipette to add 2x aliquots of 550 µl each.
3. Proteinase K (22 µl) -- stored at -20°C.
4. Blocking solution (220 µl) - stored at -20°C.
5. Probe; heat-denatured (550 µl)
6. Bead Panel 1-8 (110 µl) – each bead panel is stored at 4°C. DO NOT Freeze! It is essential to resuspend the magnetic bead panels prior to pipetting. This is done by first vortexing each panel container at setting 7 for 1 min. followed by repeated up and down pipetting prior to dispensing. Pipette the master mix multiple times as well to ensure all beads are washed out of the pipette tip.
7. Master Mix - Vortex the master mix, but try to prevent frothing of the viscous solution. Label the Greiner 384-well on side with panel information. Panel orientation should follow plate quadrant (96 well) orientation, i.e. panel 1 into Q1 (upper left hand), panel 2 into Q2 (upper right hand), panel 3 into Q3 (lower left hand), and panel 4 into Q4 (lower right hand). Panels 5-8 should be oriented in the same fashion, respectively, on a 2nd plate. Pipette by hand, 30 µl/well, each panel across the Greiner 384-well plate in appropriate wells (see above). NOTE: The solution is viscous and does not lend itself well to being processed by anything other than a pipette tip.
8. Lysate - Thaw "screening lysate plates" and in BSC hood remove solution from only Column 1 and Column 24 using vacuum suction and sterile glass pipette. The now empty wells of both Column 1 and Column 24 will receive 40 µl of HPLC-water. Transfer lysate from each screening plate to the appropriate Greiner bead panel plate using the Biomek F/X and transfer program. Place appropriate tips, plates, and plasticware including specific reagents on designated deck locations according to the program. In this context do not worry about the transfer of 50 µl. This is required due to the viscosity of the lysate solution. Heat seal the "assay plate" with ALPS 300 at 154°C for 4 seconds. Confirm seal. Place "assay plate" in appropriate shaker nest of the Cytomat 2 (54°C). Close door and activate shaker using manual input directions posted on the outside of Cytomat 2. Incubate overnight (18 hours) at 54°C at max shaking speed.

Day 2

Remove plates from shaking incubator, remove foil seal, and immediately run program, to combine all 8 quadrants from 2 overnight hybridization plates into one fresh greiner 384-well plate resting upon a magnetic stage. Add 30 µl of Pre-amplifier to each well, adhesive seal, and shake at max speed in the Cytomax2000 shaking incubator for 60 minutes at 50°C.
After hybridizing for 60 minutes, unseal the plate and place on the magnetic stage of the Biomex FX and run the wash kinome program*. Add 30 µL of Amplifier to each well, adhesive seal, and shake at max speed in the Cytomax2000 shaking incubator for 60 minutes at 50°C.
After hybridizing for 60 minutes, unseal the plate and place on the magnetic stage of the Biomex FX and run the wash kinome program*. Add 30 µL of Biotin Label Probe to each well, adhesive seal, and shake at max speed in the Cytomax2000 shaking incubator for 60 minutes at 50°C.
After hybridizing for 60 minutes, unseal the plate and place on the magnetic stage of the Biomex FX and run the wash kinome program*. Add 30 µL of SAPE reagent to each well, adhesive seal, and shake at max speed on the table top orbital platform shaker for 30 minutes at room temperature cover in tin foil to protect from light. After hybridizing for30 minutes, unseal the plate and place on the magnetic stage of the Biomex FX and run the wash kinome program*. Take plate off magnetic stage, and transfer to 96 well by running the resuspension program*. Read in the Luminex reader using program "64 plex controls last" to collect 50 beads per region in 100 µL sample volume. Bead Description: 8 x 8 Plex, Magnetic Beads, 384 well format. Colorcoded magnetic beads conjugated with specific capture probe oligonucleotide.

There are 64 color coded beads divided into 8 panels. Each panel contains 8 unique color coded beads. Each panel contains the same 8 capture oligonucleotides for the 8 x 8 assay format.
Total color coded bead: 64 color coded beads mapped to 64 regions.
Number of plex/panel & panels: 8 plex/panel & 8 panels.
Beads/ul: 500 beads/ul/plex or 4000 beads/ul/panel.
Storage condition: 4°C in the dark.

*Programs can be made available upon request.

Statistical Analysis for FUSION

The gene expression values were background corrected by subtracting the average value measured from "blank" background wells containing 40 µl of water and 30 µl of hybridization solution on each plate. The geometric mean of the control genes (PPIB and HPRT) was calculated for each sample and used to normalize the additional six reporter genes for each sample, which accounted for well-to-well signal variation. To account for probe-to-probe variation, the median for each probe across all samples was determined and used to normalize each probe measurement. The resultant values were log2 transformed. This normalization technique provided a consistent distribution of values for each probe allowing for each probe to influence the similarity metrics equally, which primarily included Euclidean distance and Pearson correlation. KSR1 funtionalogues detected by FUSION can be viewed using a Web-

based search and display tool at http://whitelab.swmed.edu/fmap/fusion1.php .

Cell Lines and Reagents

HCT116, DLD1, SW480, HCT15 and SW620 cells were purchased from American Type Culture Collection (ATCC). CBS, GEO, FET cells were kindly provided by Dr. Michael Brattain (U. Nebraska Med. Ctr.). CaCo2 cells were a gift of Dr. David Li (U. Nebraska Med. Ctr.). HCECs were a generous gift provided from Dr. Jerry Shay (UT Southwestern Med. Ctr.). HCT116, DLD1, SW480, HCT15, CaCo2 cells were grown in 37°C and 5% CO_2 in Dulbecco Modified Eagle Media (DMEM) supplemented with 10% FBS, 1% L-glutamine, 1% NEAA, and 1% penicillin/streptomycin. CBS, GEO and FET cells were grown in serum free McCoy's 5A media supplemented with vitamins, pyruvate amino acids, and antibiotics and 10 ng/ml EGF. SW620 cells were cultured in Leibovitz's L15 medium (#30-2008, American Type Culture Collection, Manassas, VA) supplemented with 10% serum and 1% penicillin/streptomycin. IEC-18 cells were cultured in DMEM, 5% FBS, 4 mM L-glutamine, and 0.15% insulin. HCECs were cultured in 37°C incubator with 2% oxygen and 5% CO_2 in Basal X medium containing 4 parts of DMEM and 1 part of Medium 199 (#11150-059, Invitrogen, Carlsbad, CA) supplemented with 10% FBS, 2% Cosmic Calf Serum (#SH 30087, Hyclone, Logan UT), 25 ng/ml of recombinant EGF (#236-EG, R&D, Minneapolis, MN). Hydrocortisone 1μg/ml (#H0888), 10 μg/ml insulin (#I550), 2 μg/ml of Apo-Transferrin (#T1428), 5 nM sodium selenite (#S5261) all from Sigma, and 50 μg/ml of Gentamicin Sulfite (#15750-060, Gibco). MG132

Antibodies and Reagents

Primary antibodies were used in the indicated dilutions: KSR1 (#H-70, Santa Cruz) 1:1000, ERRα (#V19, Santa Cruz) 1:1000, K-Ras (#F234, Santa Cruz) 1:500, α-Tubulin (#B-5-1-2, Santa Cruz) 1:2500, β-Actin (#I19,Santa Cruz) 1:1000, pMEK1/2 (#9154, Cell Signaling) 1:1000, MEK1/2 (#4694, Cell Signaling) 1:1000, pERK1/2 (#9102, Cell Signaling) 1:1000, ERK1/2 (#9106, Cell Signaling) 1:1000, pACC (#3661, Cell Signaling) 1:2000, ACC (#3676, Cell Signaling) 1:2000, pAMPKα1α2 (#2531, Cell Signaling) 1:1000, AMPKα1α2 (#2532, Cell Signaling) 1:1000, AMPKα1 (#2795, Cell Signaling) 1:1000, AMPKγ1 (#ab32382, Abcam) 1:2000, HDAC2 (#ab7052, Abcam) 1:5000, Flag-epitope (#200472, Stratagene) 1:1000, GFP (#632375,Clonetech) 1:1000, AMPKα2 (#AF2850, R&D systems) 1:1000, Ras (#OP40, EMD Millipore) 1:1000, and Actin (#A2066, Sigma) 1:1000. The PGC1β antibody was a generous gift from Dr. Ching-Yi Chang and Dr. Donald McDonell (Duke University) and was used at 1:5000 dilution. Anti-mouse, anti-goat and anti-rabbit secondary antibodies conjugated to Alexa Fluor 680 (Invitrogen, Carlsbad, CA) or IRDye800 and IRDye680RD were used at 1:5000 dilution. Recombinant AMPKα1β1γ1 (#P47-10H) and AMPKα2β1γ1 (#P48-10H) were purchased from SignalChem, Richmond BC. SAMS peptide (S07-58) was purchased from Cquential Solutions. Radioactive γ^{32}p ATP (64014) was purchased from MPBIo, MEK inhibitor U0126 (#U120) and AMPK inhibitor Compound C (#P5499) were purchased from Sigma. MEK inhibitor PD98059 (#9900) was purchased from Cell Signaling.

Gene Expression Analysis

Total RNA from cells was isolated using TRI Reagent (Molecular Research Centers, Inc) and its quality was analyzed using a Bioanalyzer (Agilent). 2.5µg of total RNA was reverse transcribed to generate cDNA using Affymetrix 1-cycle Target Labeling kit. The resulting cDNA was hybridized to HG_U133 Plus 2.0 arrays and scanned on a Gene Chip scanner 3000 7G (Affymetrix) in triplicate. The .cel files containing gene expression data were processed together using Robust Multichip Averaging with the program Expression File Creator, hosted by GenePattern, to create a .res file. That .res file was analyzed using Gene Set Enrichment Analysis (GSEA) (BROAD Institute) (*13*). Cutoff for significant gene set enrichment was set at NOM p-value< 0.05, a FWER p-value< 0.05, and a FDR q-val< 0.25.

In Situ hybridization Processing Details and Analysis

Formalin fixed and paraffin embedded human colon tumor microarray slides prepared by the Tissue Sciences facility at the University of Nebraska Medical Center were used for the study. TMA slides were baked overnight at 60° C. Then the slides were fixed in 10% formaldehyde, deparaffinization by xylene, followed by boiling the tissues in 1X pretreatment solution for 10 minutes and protease digestion for 10 minutes. Tissues were again fixed in 4% formaldehyde followed by hybridization with probe sets at 40°C for 2 hours. Tissues were then washed in wash buffer and stored overnight in storage buffer. The following day the TMAs were hybridized to preamplifier solution, followed by amplifier solution. The tissues were then hybridized to the labeled probe and the signal was developed by adding the fast red substrate and counterstaining with DAPI. Control slides were generated using the same procedure while excluding the addition of the probes. These slides were used to control for nonspecific binding of the fast red substrate.

Image acquisition and analysis

Images were acquired with a fluorescent microscope (Leica DM 5500B) using TX680 filter. Further analysis was performed using ImageJ and MetaMorph (Molecular Devices, Sunnyvale, CA). Patient samples were included in triplicate on the tissue microarrays (TMA). Each sample was photographed, which resulted in three representative images for each patient. To quantify mRNA only within the colonic epithelial cells, three epithelial regions from each image were selected manually and the regions of interest were drawn by hand and recorded using MetaMorph. Individual mRNA (each represented by single red dot) was counted for each region of interest. To account for nonspecific binding of the fast red substrate, the background was calculated by averaging the red puncta staining for all control images from a TMA, then subtracted from the RNA expression count for each image. RNA expression was normalized by cell number, which was quantified by counting the DAPI-stained nuclei within each region of interest. The normalized target RNA count represents the average amount of mRNA per nuclei within each image. These measurements were then averaged across the triplicate images for a given patient. The fold change in target RNA per nuclei was calculated by dividing each

patient's mRNA per nuclei by the average of all of the normal patient samples. Significance was evaluated by calculating an unpaired two-sided t-test.

TABLE S1: Sequences of shRNA oligonucleotides

shRNA	Sequences
shKSR1	5' GTGCCAGAAGAGCATGATTTT 3' 5' GCTGTTCAAGAAAGAGGTGAT 3'
shPGC1β	5' CCCTCGAGGAATACCTCAATA 3' 5' CCTGAGTATGACACTGTCTTT 3' 5' GCATAGTCTAGGCAAAGAAAT 3'
shERRα	5' CGCAGAGCAATAACACTATATT 3' 5' ACCCTGCAGAGCAATAACACTA 3'

TABLE S2: Sequences of siRNA oligonucleotides

siRNA	Sequences
siKSR1	5' AGAAAGAGGUGAUGAACUA 3' 5' GGAAUGAAGCGUGUCCUGA 3' 5' GAGCAAGUCCCAUGAGUCU 3'
siK-Ras	5' GGAGGGCUUUCUUUGUGUA 3' 5' UCAAAGACAAAGUGUGUAA 3' 5' GAAGUUAUGGAAUUCCUUU 3'
siAMPKγ1	5' GAGAAGAAGCCUGAGCUG 3' 5' GGAACAAGAUCCACAGGCU 3' 5' UCAAUAUCCUGCACCGCUA 3' 5' GAGGUUCACCGACUUGUAG 3'
siAMPKα1	5' GCCCAGAGGUAGAUAUAUG 3'
siAMPKα2	5' GACAGAAGAUUCGCAGUUU 3'
siERK1	5' GACCGGAUGUUAACCUUUA 3' 5' CCUGCGACCUUAAGAUUUG 3' 5' CCAAUAAACGGAUCACAGU 3' 5' AGACUGACCUGUACAAGUU 3'
siERK2	5' UCGAGUAGCUAUCAAGAAA 3' 5' CACCAACCAUCGAGCAAAU 3' 5' GGUGUGCUCUGCUUAUGAU 3' 5' ACACCAACCUCUCGUACAU 3'
siERRα	5' GGCCUUCGCUGAGGACUUA 3' 5' GCGAGAGGAGUAUGUUCUA 3'
siPGC1β	5' CCAGAAGGCGUCCUGCAAA 3'

TABLE S3: Sequences of qPCR primers:

Primers	Sequences
PGC1β (F)	5’ CGCTTTGAAGTGTTTGGTGAGATTG 3’
PGC1β (R)	5’ GCTGGAAGGAGGGCTCGTTG 3’
ERRα (F)	5’ CACTATGGTGTGGCATCCTGT 3’
ERRα (R)	5’ CGTCTCCGCTTGGTGATCTC 3’
GAPDH (F)	5’ GGTGAAGGTCGGAGTCAACGG 3’
GAPDH (R)	5’ GAGGTCAATGAAGGGGTCATTG 3’