**Supplementary Materials and Methods**

**Cell authentication**. Two hyper variable regions (HVR1: 50-585 bp, HVR2: 16005-16503 bp) of mitochondrial genome of the revised Cambridge Reference Sequence (rCRS) were used for the cell line authentication [1]. These sequences are commonly used for cell line authentication by other investigators [2]. PCR products were sequenced at the UCLA genome sequencing core facility, and the data showed the presence cell specific SNPs (single nucleotide polymorphisms).

**FACS analysis**. Briefly, cells at 70% confluency were transfected with control or PACS-1 siRNA (On-Target plus individual or smart pool of 4 siRNAs in a single reagent mix (Catalog numbers of individual siRNAs: J-006697-09-0010, J-006697-10-0010, J-006697-11-0010, J-006697-12-0010 and that of Smart pool: L-006697-01-0020) from Dharmacon, Inc., Lafayette, CO) using the lipofectamine (Invitrogen, Carlsbad, CA) following the manufacturer's protocol. Hsa-miR-Control, hsa-miR-34a or hsa-miR-49a alone or in combination with PACS-1 or LNA-anti-miR-449a was transfected using the RNAi transfection reagent (Invitrogen, Carlsbad, CA). Forty-eight hours post-transfection, cells were treated with trypsin, washed with 1X PBS and stained with Propidium iodide (PI). Annexin staining was carried out using the annexin staining kit (Beckton Dickinson, San Jose, CA) following the manufacturer's protocol. Cells were analyzed for cell cycle and annexin staining for apoptosis by FACS (Flowcytometry core facility) and data were analyzed using the standard software program.

**Western blot analysis**. Proteins were extracted from cells using m-RIPA buffer or cytoskeletal (CSK) buffer (cell fractionation studies) after washing the cells twice with cold PBS. Proteins were normalized for their concentration and denatured using 4X SDS-PAGE sample buffer followed by heating to 100°C for 10 minutes. Proteins were separated on SDS-PAGE gels, transferred onto nitrocellulose membranes, and hybridized to antibodies as indicated [3]. Membranes were developed using chemiluminescence and the relative intensities were determined by densitometry using Image J software. The antibodies used were; anti Lamin

A/C antibody (sc-376248), anti-p53 (sc-126), anti-p21(sc-817), anti-beta actin (sc-8432), anti-SIRT1 (sc-15404), and anti-beta tubulin (sc-9104) (Santa Cruz Biotechnology, Inc., Dallas, TX), anti-acetylated (K-382)-p53 (Cat # 2525, Cell Signaling, Bedford, MA), anti-phospho H2AX (Ser-139, Cat # 2577, Cell Signaling), anti-phospho-Chk1 (Ser-317) (Cat # 2344, Cell Signaling), anti PACS-1 (sc-136344) ( Santa Cruz Biotechnology) and anti PACS-1 601 and 17703 raised in rabbits (donated by Dr. Gary Thomas, University of Pittsburgh, PA). Western blots were carried out with 1:1000 dilution of the antibodies as described earlier [3, 4].

**3′-UTR constructs/luciferase assay**. HeLa and SiHa cells were seeded at $2.5x10^5$ cells per well in 6-well plates. 24 hours later, pMIR-REPORT Luciferase plasmid vector (Origene Technologies, Rockville, MD), including 3′-UTR of PACS1 (WT or mutant vector, 500 ng), β-galactosidase (100 ng) and precursor hsa-miR-34a (30nM), precursor hsa-miR-449a (30nM), or precursor miRNA control (30nM) were transfected by using siPORT NeoFX transfection reagent and the luciferase assays were performed as described [5].

**Analysis and quantification of miRNA expression**. For both mRNA and microRNA quantification, total RNA was isolated with the mirVana miRNA Isolation Kit (Ambion, AM1561) per manufacturer's instructions. For microRNAs analysis, RNA was reverse transcribed using the TaqMan microRNA reverse transcription kit (Life Technologies -Sigma Aldrich, St. Louis, MO) and the expression assays were performed using quantitative real time -PCR utilizing TaqMan expression assay with miRNA-specific primers using 20ng RNA (Life Technologies) on the QuantStudio 12K Flex Real-Time System. RNU48 was used as an endogenous control to normalize expression [5]. For PACS1 mRNA expression analysis, TaqMan gene expression assay was performed using PACS1 specific primers and ACTB (β-actin) gene specific primers as endogenous expression control.

**Luciferase assay.** Luciferase assays were performed using the dual-light system reporter assay system (Applied Biosystems - Thermo-Fisher Scientific, Waltham, MA) for combined detection of firefly luciferase and β -galactosidase 48 hours' post transfection [5]. Relative luciferase

expression was determined with respect to β-galactosidase control in the transfected cell lines. Wild type PACS-1 3' UTR plasmid containing the hsa-miRNA 34a/449a binding sites were derived from UC Santa Cruz GRCH 38/hg sequence chr11: 66,243,283 CCTG… CACTGCCA....CACTGCCA… CCCT 66,243,450. Mutant sequences contained 4bp substitutions (indicated by underlined green letters) at the two miRNA binding sites CCTG…CACCAAGA…. CACCAAGA…CCCT.

**EdU labeling assay.** Cells were grown to 70% confluency and split 1:2 after 24 hours and after a further 36 hours, treated with RPMI medium containing EdU (10ug/ml) for a 2-hour pulse labeling. EdU medium was replaced with regular RPMI medium and grown for 10 hours for the 2-hour pulse + 10-hour chase condition. Cells collected at 2 hours (pulse) and at 2 + 10 hours (chase) were subjected to FACS analysis using the manufacturer's (Click-IT$^{TM}$ Plus EdU Alexa Fluor$^{488}$ Flow Cytometry Assay Kit, C10432) and PI/RNase (FxCycle, Molecular probes, Catalogue no. F10797) staining protocol. Samples were then analyzed by the SORP BD LSRII Analytic Flow Cytometry instrument at UCLA FACS Core Facility. The FACS files were analyzed by Flow Jo and Mod Fit software. For the immunofluorescence analysis, control or PACS-1 siRNA transfected cells treated with EdU (2-hour pulse and 2-hour pulse + 8-hour chase) were grown in slides.

**Beta-galactosidase activity.** Control (untransfected) and transfected cells were grown for 72 hours and stained for Beta-galactosidase using the staining kit from Cell Signaling (Cat # 9860, Cell Signaling, Bedford, MA). Stained cells were photographed at different magnifications using the Zeiss microscope [3].

**Immunofluorescence**. Briefly, exponentially growing cells were transfected with indicated siRNAs, miRNAs, and plasmid vectors. Transfected cells were seeded onto LabTek chamber slides and 48 hours' post-transfection, cells were exposed to CPT (Cat # 7689-03-4, Sigma-Aldrich Chemical Co, St. Louis, MO) or etoposide (E1383, Sigma-Aldrich Chemical Co) and doxorubicin (D1515, Sigma-Aldrich Chemical Co) as indicated (control cells received DMSO).

Cells were washed twice with cold PBS, permeabilized using PBS-T (PBS with 0.2% Triton X-100) and fixed in 3% paraformaldehyde for 10 minutes and then in 100% methanol (-20 °C) for additional 10 minutes. Non-specific binding was blocked using 10% goat serum and stained with primary antibodies [3, 4] followed by fluorescent conjugated secondary antibodies. Stained cells were observed under Zeiss or Nikon confocal microscopes and the images were captured and processed using the software provided by the manufacturer.

**RNA isolation, library construction and RNA-seq gene differential analysis.** RNAs were isolated from control or siRNA transfected cells using a pure Link RNA mini kit from Ambion (12183018A; Life Technologies, Inc., Carlsbad, CA) and the libraries were made per well-established Illumina Ribo-zero protocol. Six barcoded libraries were multiplexed and sequenced on one lane of illumina HiSeq sequencer. Reads with perfect tags were demultiplexed and mapped to human genome hg19 with refseq gene annotation by tophat2(version 2.0.6) together with bowtie1(version 0.12.8) [6]. Uniquely mapped reads were used by Htseq-count to calculate the number of reads that aligned to each refseq gene and DESeq2 (version 1.4.5) was used to perform gene differential expression analysis [7, 8] .

**Whole genome library preparation and aneuploidy analysis.** Purified genomic DNA from 48 hours post control or PACS-1 siRNA or PACS-1 and p53 siRNAs transfected fibroblast cell line GM00023 or HeLa cells were quantified using Qubit dsDNA HS. Libraries were prepared using SparQ DNA Frag Library Prep kit (Quanta Bio - Beverly, MA, USA) according to manufacturer's protocol. Briefly, 100 ng of DNA was fragmented and end-repaired for 15 minutes at 32℃ followed by 30 min at 65℃. Ligation was performed using Illumina TruSeq Single Index Adapters (cat # 20015960 and 20015961 - Illumina, San Diego, CA, USA). The final PCR was performed according to manufacturer's instructions for a total of 5 PCR cycles. Final libraries were sequenced as 1x50 on a HiSeq3000 (llumina, San Diego, CA, USA). Sequenced reads were aligned to Human hg19 genome with Bowtie -m 1 option which discards any reads that are not uniquely mapped to the genome. Duplicated reads were removed and CNV plot was

generated. CNV-Seq software was used to determine genomic regions with copy number variations using parameters -p-value 0.0001 -bigger-window 10 -global-normalization as suggested [9, 10].

**Cervical cancer survival analysis.** TCGA-CESC (cervical cell squamous cell carcinoma) RNAseq expression data and survival phenotype data was downloaded from UC Santa Cruz Cancer Browser (http://xena.ucsc.edu) using Toil platform [11]. Only samples which had both gene expression and survival data were included. Expression data is RNA sequenced counts, normalized using the log2(fpkm-uq+1) upper quantile, normalized for gene size) and was then dichotomized by the cohort median values using R and rendered using R CRAN survminer package. Original data derived from GDC TCGA Cervical Cancer (CESC) available at https://gdc.cancer.gov/" version: "09-15-2017", processed on Illumina platform.

**References**


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