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| **Key Resources Table** |
| **Reagent type (species) or resource** | **Designation** | **Source or reference** | **Identifiers** | **Additional information** |
| Primary cells (Human) | Human Umbilical Vein Endothelial Cells (HUVEC) | This paper |   | See Materials and Methods |
| cell line (Human) | 293T | ATCC | CRL-3216 |  |
| antibody | Rabbit monoclonal anti-VEGFR2 clone 55B11 |  Cell Signaling Technology |  2479 | 1:1000 |
| antibody | Mouse monoclonal anti-GAPDH [6C5] | Abcam | ab8245 | 1:1000 |
| antibody | Rabbit monoclonal anti- P38 | Cell Signaling Technology | 9212 | 1:1000 |
| antibody | Rabbit monoclonal Phospho-p38 MAPK(Thr180/Tyr182) (D3F9) XP | Cell Signaling Technology | 4511 | 1:1000 |
| antibody | Rabbit monoclonal anti- ERK1/2 p44/42 MAPK (Erk1/2) (137F5)  | Cell Signaling Technology | 4695 | 1:1000 |
| antibody | Mouse monoclonal Phospho-p44/42 MAPK (Erk1) (Tyr204)/(Erk2) (Tyr187) (D1H6G) | Cell Signaling Technology | 5726 | 1:1000 |
| antibody | Rabbit polyclonal anti-DLL4 | Abcam | ab7280 | 1:1000 |
| antibody | Goat polyclonal anti-CXCR4 | Abcam | ab1670 | 1:1000 |
| recombinant DNA reagent | MISSION® pLKO.1-puro Non-Target shRNA Control | Sigma-Aldrich |  SHC016 |   |
| recombinant DNA reagent | MISSION® shRNA Bacterial Glycerol Stock SHCLNG06271709MN (DICER1 shRNA #3) | Sigma-Aldrich | NM\_030621.3-315521C1 TRCN 0000290426 |  |
| recombinant DNA reagent | MISSION® shRNA Bacterial Glycerol Stock SHCLNG06271709MN (DICER1 shRNA #4) | Sigma-Aldrich | NM\_030621.3-315521C1 TRCN 0000512611 |  |
| recombinant DNA reagent | pWPT-12XCSL-DsRedExpressDR | This paper |  | See Materials and Methods |
| recombinant DNA reagent | pLVX-DsRed-Express2-N1 | Takara | 632560 |  |
| chemical compound, drug | SCH 772984  | Cayman Chemical | S7101 |  |
| chemical compound, drug | SB 202190  | Sigma-Aldrich | S7067 |  |
| chemical compound, drug | DAPT | Sigma-Aldrich | D5942 |  |
| chemical compound, drug | 5-Phospho-D-ribose 1-diphosphate pentasodium salt | Sigma-Aldrich | P8296 |  |
| chemical compound, drug | L-[14C(U)]-Glutamine | Perkin Elmer | NEC4510 |  |
| chemical compound, drug | [14C]-NaHCO3 | Perkin Elmer | NEC086H00 |  |
| chemical compound, drug | Aminoimidazole-4-carboxamide ribonucleotide | Sigma-Aldrich | A9978 |  |
| chemical compound, drug | 5-Formyl-5,6,7,8-tetrahydrofolic acid calcium salt hydrate | Sigma-Aldrich | COM945512397 |  |
| chemical compound, drug | L-serine | Sigma-Aldrich | S4500 |  |
| chemical compound, drug | Serine-hydroxy-methyltransferase, human recombinant | BOSTER BIOLOGICAL TECHNOLOGY | PROTP34896 |  |
| chemical compound, drug | Methylene-tetrahydrofolate reductase, human recombinant | Origene | TP308588 |  |
| chemical compound, drug | β-Nicotinamide adenine dinucleotide 2′-phosphate reduced tetrasodium salt hydrate | Sigma-Aldrich | N1630 |  |
| chemical compound, drug | L-serine | Sigma-Aldrich | S4500 |  |
| chemical compound, drug | Mitomycin C from Streptomyces caespitosus | Sigma-Aldrich | M4287 |  |
| peptide, recombinant protein | Recombinant Human VEGF 165 Protein | R&D Systems | 293-VE-010 |  |
| peptide, recombinant protein | Recombinant Human DLL4 His-tag | R&D Systems | 1506-D4 |  |
| Other | Heparin sodium salt from porcine intestinal mucosa | Sigma-Aldrich | H3393 |  |
| Other | Collagen, Type I solution from rat tail | Sigma-Aldrich | C3867 |  |
| Other | Collagenase A from Clostridium histolyticum | Sigma-Aldrich | COLLA-RO |  |
| Other | TRIzol™ Reagent |  ThermoFisher Scientific | 15596026 |  |
| Other | RNAiMAX lipofectamine |  ThermoFisher Scientific | 13778075 |  |
| Other | Methylcellulose | Sigma-Aldrich | M7027 |  |
| sequence-based reagent | mirVana™ miRNA Mimic Negative Control #1  | ThermoFisher Scientific |  4464059 |   |
| sequence-based reagent |  mirVana™ miRNA Inhibitor Negative Control #1 | ThermoFisher Scientific |  4464077 |   |
| sequence-based reagent |  mirVana® miRNA mimic hsa-miR-29a-3p | ThermoFisher Scientific |  MC12499Cat No 4464066 |   |
| sequence-based reagent | mirVana® miRNA inhibitor hsa-miR-29a-3p | ThermoFisher Scientific |  MH12499Cat No 4464085 |   |
| sequence-based reagent |  mirVana® miRNA mimic hsa-miR-424-5p | ThermoFisher Scientific |  MC10306Cat No 4464067 |   |
| sequence-based reagent | mirVana® miRNA inhibitor hsa-miR-424-5p | ThermoFisher Scientific | MH10306Cat No 4464085 |   |
| sequence-based reagent | mirVana® miRNA mimic hsa-miR-16-5p | ThermoFisher Scientific | MC10339 Cat No 4464067 |   |
| sequence-based reagent | mirVana® miRNA inhibitor hsa-miR-16-5p | ThermoFisher Scientific | MH10339Cat No 4464085 |   |
| commercial assay or kit |  Click-iT® EdU Flow Cytometry Cell Proliferation Assay |  ThermoFisher Scientific |  C10425 |   |
| commercial assay or kit |  Taqman PCR Universal MasterMix |  ThermoFisher Scientific |  4364338 |   |
| commercial assay or kit |  High Capacity cDNA Reverse Transcription kit |  ThermoFisher Scientific |  4368814 |   |
| commercial assay or kit | TaqMan™ Advanced miRNA Human A Card | ThermoFisher Scientific | A34714 |  |
| commercial assay or kit | TaqMan™ Advanced miRNA cDNA Synthesis Kit | ThermoFisher Scientific | A28007 |  |
| commercial assay or kit |  miRNeasy Mini Kit | Qiagen |  217004 |   |
| commercial assay or kit |  RNase-Free DNase Set | Qiagen |  79254 |   |
| commercial assay or kit |  Agilent RNA 6000 Nano Kit | Agilent Technologies |  5067-1511 |   |
| commercial assay or kit  | Illumina™TotalPrep™RNA Amplification Kit | ThermoFisher Scientific | AMIL1791 |  |
| commercial assay or kit | HumanHT-12 V4 Beadchip kit | Illumina | BD-103-0204 |  |
| commercial assay or kit | Pierce™ BCA Protein Assay Kit | ThermoFisher Scientific | 23225 |  |
| commercial assay or kit | MAP Kinase (Total Protein) Whole Cell Lysate Kit  | Meso Scale Diagnostics | K15157D-1 |  |
| commercial assay or kit | MAP Kinase Whole Cell Lysate Kit | Meso Scale Diagnostics | K15101D-1 |  |
| commercial assay or kit | CIM-Plate16 | ACEA Biosciences | 5665817001 |  |
| commercial assay or kit | Qubit RNA HS Assay Kit | ThermoFisher Scientific | Q32852 |  |
| software, algorithm | 2100 Expert | Agilent Technologies | Version 2.6 |  |
| software, algorithm | Genome Studio | Illumina | GSGX Version 1.9 |  |
| software, algorithm | ImageJ | NIH | Version 1.51n |  |
| software, algorithm | Prism | GraphPad | Version 7 |  |
| software, algorithm | Summit | Dako | Version 5 |  |
| software, algorithm | Leica Application Suite | Leica | Version X |  |
| software, algorithm | Image Lab | Biorad | Version 5.2.1 |  |
| software, algorithm | GSEA | Broad Institute | Version 2.2.3 |  |
| software, algorithm | Cytoscape | Cytoscape.org | Version 3.3.0 |  |
| software, algorithm | Bowtie2 | http://bowtie-bio.sourceforge.net/bowtie2/index.shtml |  | Langmead et al., 2009 |
| software, algorithm | RSEM | http://deweylab.github.io/RSEM/ |  | Li and Dewey, 2011 |
| software, algorithm | DESeq2 | https://bioconductor.org/packages/release/bioc/html/DESeq2.html |  | Love et al. 2014 |
| software, algorithm | FASTX-Toolkit | http://hannonlab.cshl.edu/fastx\_toolkit/ |  |  |
| software, algorithm | BWA | http://bio-bwa.sourceforge.net |  | Li and Durbin, 2010 |
| software, algorithm | The R Project for Statistical Computing | https://www.r-project.org/ |  |  |
| software, algorithm | MATLAB | MathWorks | Version R2018a |  |
| software, algorithm | MATLAB codes | http://tuvalu.santafe.edu/~aaronc/powerlaws/ |  |  |