**Supplemental Information**

**Supplemental Figure S1.** Top canonical pathways associated with WSB1 expression. Differentially expressed genes associated with canonical pathway in INGENUITY pathway analysis. Total RNA were extracted from 56 pairs of fresh-frozen (FF) primary never smoker lung adenocarcinomas and analyzed by WSB1 status using INGENUITY pathway analysis (see Supplemental Experimental Procedures.)

**Supplemental Figure S2.** Top biological functions associated with WSB1 expression. Gene expression profiles using total RNA from 56 pairs of fresh-frozen (FF) primary never smoker lung adenocarcinomas and analyzed by WSB1 status using INGENUITY pathway analysis (see Supplemental Experimental Procedures.)

**Supplemental Figure S3.** Metastasis-free survival in breast and colon cancer patients. (A-C) Kaplan–Meier graph of (A) metastatic human breast cancer, (B) breast cancer metastasis to brain and (C) metastatic colon cancer patients stratified according to high or low expression levels of WSB1 (PROGgene).

**Supplemental Figure S4.** WSB1 interacts and negatively correlated with pVHL. (A) Co-immunoprecipitation (Co-IP) of exogenous HIF-1α (HA), pVHL (HA) and WSB1 (Myc) from extracts of HEK 293T cells. * indicates non-specific band. (B) Five lung, six pancreatic, four breast cancer cell lines and normal MCF10A cells were analyzed by immunobloting for indicated proteins.
**Supplemental Figure S5.** HIF-1α level and target gene’s expression were decreased in cells depleted of WSB1. (A) Representative images of HIF-1α protein expression in HeLa cells. Cells were transfected with WSB1 shRNA (#1 or #2) (GFP positive) and then stained with DAPI (blue for DNA) and anti-HIF-1α (red). Infected cell by WSB1 shRNA are indicated by white arrowheads. The scale bar represents 10 μm. (B) Cells were infected with WSB1 shRNA (#2) and then collected for qPCR analysis. *, $P<0.05$, **, $P<0.01$ versus Control shRNA by one-way ANOVA.

**Supplemental Figure S6.** The correlation between WSB1 and HIF target genes expression in metastatic colon and urinary bladder cancer patients (GEO data set. Table S1)

**Supplemental Figure S7.** WSB1 interacts with pVHL in hypoxia mimic conditions. (A) Cells were treated with CoCl2 and MG132 and then collected for immunoprecipitation (IP) and immunoblot analysis. (B) Cells were infected with HIF-1α shRNA and then collected in hypoxic or normoxic conditions. S.E. , short exposed; L.E., long exposed. (C) HIF-1α, HIF-2α, pVHL and WSB1 protein levels were examined after CoCl2 treatment without MG132.

**Supplemental Figure S8.** WSB1 promotes cancer cell invasion and migration by enhance HIFs. (A) Cells were transduced with or without the viral vectors indicated and collected for immunoblot analysis. (B) Trans-well invasion assay of 786-O or 786-O/VHL cells stably expressing the indicated shRNAs or plasmids. The plot shows quantification of the area covered by the invasion cells, relative to the control. The results represent the means (±S.E.) of three independent experiments performed in triplicate. **, $P<0.01$ versus vector virus injected cells; *, $P<0.05$ versus Control shRNA infected cells by one-way ANOVA. (C) Quantification of wound-healing assays of 786-O or 786-O/VHL cell lines stably transfected
with the indicated plasmids or shRNA. The mean and s.d. of one representative experiment, out of three independent experiments performed in triplicate, are shown (***, \(P < 0.001\) versus vector virus injected cells by one-way ANOVA). (D) Representative images in Supplemental Figure S8C. (E and F) Lentiviral-driven shRNA was used to deplete endogenous WSB1 and rescue with an RNAi-resistant WSB1 (Wt or \(\Delta SOCS\)) in MDA-MB-231 cells. (E) HIF-1\(\alpha\) activity. The results represent the means (±S.E.) of three independent experiments performed in triplicate. ***, \(P < 0.001\) versus Control shRNA virus infected cells; ****, \(P < 0.0001\) versus WSB1 shRNA infected cells by one-way ANOVA. (F) Cells as in (E) were then collected for immunoblotting with the indicated proteins. Exo, Exogenous; Endo, Endogenous. (G) Representative images of wound healing experiments. Lentiviral-driven shRNA was used to deplete endogenous WSB1 and rescue with an RNAi-resistant WSB1 (Wt or \(\Delta SOCS\)) in RCC4/VHL cells.

**Supplemental Figure S9.** WSB1 regulates HIF-1\(\alpha\) in a HIPK2 independent manner. Left: Cells were infected with indicated shRNA and were assayed by wound healing experiments. Right: The expression of indicated proteins was examined by immunoblotting.

**Supplemental Figure S10.** WSB1 promotes cancer cell metastasis and negatively correlated with pVHL in tail vein metastasis. (A) Lung colonization assay of mice intravenously injected with B16F10 cells stably infected with the indicated viral construct or shRNA. Top: Representative lung organs were shown. Middle: The plot shows the number of metastatic foci per section. ***, \(P < 0.01\) by one-way ANOVA. Bottom: Cells as in (Top) were then collected for immunoblot analysis. Exo, Exogenous; Endo, Endogenous. (B-D) Lung or liver colonization assay of mice intravenously injected with B16F10 cells stably infected with the indicated viral construct or shRNA. (B) Representative lung organs or liver were shown. (C)
The plot shows the number of metastatic foci per section. (D) Cells as in (B) were then collected for immunoblot analysis. Exo, Exogenous; Endo, Endogenous. *, $P<0.05$, **, $P<0.01$, ***, $P<0.001$ versus control cells by one-way ANOVA.

**Supplemental Table 1.** The GEO Dataset.

**Supplemental Table 2.** Differentially expressed meta_related genes by WSB1 status in never-smoker lung adenocarcinoma.
Supplemental Methods

Plasmids.

Myc-tagged WSB1 (empty and WT, ∆WD1-2, ∆WD1-3, ∆N, ∆SOCS and ∆C) were kindly provided by Dr. Cheol Yong Choi (Sungkyunkwan University, Korea)(Choi et al. 2008). HA-tagged HIF-1α and HA-tagged VHL (Wt, C162F and R167W) were obtained from Addgene.

Transient Transfection and Stable Transduction.

shRNAs were infected using Lipofectamine 2000 reagent (Invitrogen). Human WSB1, mouse WSB1, HIF-1α, HIPK2, Cullin2 and 5 were obtained from Sigma-Aldrich and Open Biosystems.

**WSB1** shRNA (human) : Open Biosystems

5’- TGCTGTGGACAGTGAGCGGGAGTTTCTCTCGTATCGTATTAAGATGAAGGCGACATAGGAAGGCCACAGA TGTAATACGATACGAGAGAACTCCATGCCTACTGCGCTCGGA -3’

5’- TGCTGTGGACAGTGAGCGCGCTG TAAAGTGCAAGGAAATTTAGTGAAGGCCACAG ATGTAATTTTCTTCTTCAGCATGCGCTACTGCTCGGA -3’

**WSB1** shRNA (Mouse) : Sigma-Aldrich

5’- ACATGAGCTGCTGCTATATATA -3’

5’- GCTTTACTCCTTTGTATCAGGCTT -3’

**HIF-1α** shRNA (Mouse) : Sigma-Aldrich

5’- GTGATGAAAGAATTACCGAAT -3’

5’- TGCTCTTTGTGGATCTA -3’

**HIPK2** shRNA (Mouse) : Open Biosystems

5’- GCTGTGGACAGTGAGCGCGACGAGTACGTATCCAGCCCAATTAGTGAAGGCCACA
GATGTAATTGGGCTGGATACTGACTCGGTGCCTACTGCCTCGGA -3’
5’-GCTGTTGACAGTGAGCGAGGAGAGTGCCGATGACTATAATAGTGAAGCCACA
GATGTATTATAGTCATCGGCACCTCTCCGTGCCTACTGCCTCGGA -3’

_Culllin 5_ shRNA (human) : Sigma-Aldrich
5’-GCTAGAATGTTCAGGACATA -3’
5’-CGCTGTATTGTTTGCATGGAA -3’
5’-GCAGACTGAATTAGTAGAAAT -3’
5’-GCAGTTAAACTTGCCAAATATA -3’
5’-GCCATCAAGATGATACGGCTT -3’

_Culllin 2_ shRNA (human) : Sigma-Aldrich
5’-GCAAGCTACATCGGATGTATA -3’
5’-GCCCTTATTCAAGAGGTGATT -3’
5’-CGTTTGCGATGTGTCTT -3’
5’-CCCTTGAGAAAGACTTTATA -3’
5’-GCAGACTATATGGACTGCTTA -3’

For transient overexpression studies, DNA plasmids were transfected using Lipofectamine 2000 reagent (Invitrogen). Stable overexpression and silencing were obtained by transducing MDA-MB-231 cells, HEK 293T, HEK 293, RCC4, RCC4/VHL, 786-O, 786-O/VHL and H1299 cells with retroviral or lentiviral vectors. The efficiency of knockdown or overexpression was controlled by Western Blotting.

_Migration and Invasion Assays._
For migration assays (wound healing assays), cells were seeded in 6-well plates at a density of 15 % / well and grown until confluence (around 3 days). And then complete medium replaced by serum-free medium, for 24 h. Confluent cells (monolayer) was scraped with a P200 tip in each well (3 lines/well), the medium was replaced with complete medium. After 24 ~ 48 h the cells were fixed with 3.7 % Paraformaldehyde. Photographs were obtained at 0, 1 and 2 days. Cell migration was quantified by counting inside the scratch (at time 0 as standard) in each different fields of the wound.

For matrigel invasion assays, RCC4 or RCC4/VHL and 786-O or 786-O/VHL cells were infected with shRNAs in 10cm dishes. After 8 h, the medium was changed to serum-free medium and grown until ~80 % confluence. Cells were seeded in 24-well invasion chamber (Corning, 354480). Each sample was plated in triplicate (500,000 cells/ insert). All protocol was followed as recommended standard protocol. To measurement of cell invasion, the filter was stained with 0.2 % Crystal Violet and invasion cells were counted.

Coimmunoprecipitation Assays, Immunobloting and Antibodies.

To study endogenous WSB1/pVHL binding, the cells were treated with or without 10 μM MG 132 (Sigma) for 2 hours. Cells was lysed by sonicator in NETN buffer (20 mM Tris-HCl, pH 8.0, 100 mM NaCl, 1mM EDTA, 0.5 % Nonidet P-40) containing 50 mM b-glycerophosphate,10mM NaF, and 1 mg/ml each of pepstatin A and aprotinin, freshly supplemented with protease inhibitor cocktail (Roche). Prior to immunoprecipitation, protein A-bound Agarose beads were incubated overnight with pVHL (Cell signaling, #2738), WSB1 antibody (Abcam, ab68953; Sigma, HPA003293; Proteintech, 1166-1-AP), HIF-1α antibody (Abcam, ab51608), Cullin2 (Abcam, ab166917) and Cullin 5 (Abcam, ab34840) in PBS with 5 % BSA at 4 °C. We use
ab68953 for most of data (HPA003293 for IHC). We then added to the extracts before immunoprecipitation with protein-A agarose at 4°C for 4 hours. After three washings in binding buffer, co-purified proteins were analyzed by Western Blotting.

For ubiquitination assays, HEK 293T cells were infected with the indicated shRNAs or HA-tagged VHL (Wt, C162F and R167W) with His-ubiquitin. Before harvesting, cells were treated for 4 hours with proteasome inhibitor 10 μM MG 132 (Sigma). After we performed the ubiquitination assays as described previously (Yuan et al. 2010).

For removing heavy chain, heavy or light-chain-specific anti-mouse and anti-rabbit IgG secondary antibodies were obtained from Jackson Immunoresearch. Rabbit polyclonal antibodies recognizing HIF-2α (Novus, NB100-122), were purchased from Novus. For removing heavy chain, heavy or light-chain-specific anti-mouse and anti-rabbit IgG secondary antibodies were obtained from Jackson Immunoresearch.

**Immunofluorescence.**

For immunofluorescence staining, HeLa cells were plated on glass cover slips and transfected with the indicated constructs. Cells were then fixed in 3.7 % paraformaldehyde for 10 min at room temperature and stained using standard protocols. Immunofluorescence images were taken using fluorescent microscopy (Nikon Microscope, Melville, New York).

**Real time PCR or Reverse Transcription (RT)-PCR of cDNA.**

RNA preparation, cDNA, and qRT-PCR were described previously (Lee et al. 2011). The following primers were used:

*HIF-1α* Forward 5’- CATGGAAGGTATTGCACTGC-3’,
Reverse 5’-CACACATACAATGCACTGTGG -3’,

**VEGFA** Forward 5’-CCTTGCCCTTGCTGTCTACCTC-3’,

Reverse 5’-TTCTGCCCTCCTCCTTCTGC-3’,

**CA90** Forward 5’-CAATATGAGGGGTCTCTGACTACAC-3’,

Reverse 5’-GGAATTCAGCTGGACTGGCTCAGC -3’,

**ALDOC** Forward 5’-GCGCTGTGTGCTGAAAATCAG-3’,

Reverse 5’-CCACAATAGGCACAATGCCATT-3’,

**SAP30** Forward 5’-AGTTGGTTGCCACTTTAGGTC-3’,

Reverse 5’-CCACGTCTCCTAGTGAACACC -3’,

**GULT1** Forward 5’-TCATCGTGGCTGAACTCTTCAG-3’,

Reverse 5’-TCACACTTGGGAATCAGCCCC-3’,

and **β-actin** sequence were described previously (Lee et al. 2011).

**Supplemental References**

Choi DW, Seo YM, Kim EA, Sung KS, Ahn JW, Park SJ, Lee SR, Choi CY. 2008. Ubiquitination and degradation of homeodomain-interacting protein kinase 2 by WD40 repeat/SOCS box protein WSB-1. *The Journal of biological chemistry* **283**: 4682-4689.

Lee SB, Kim JJ, Chung JS, Lee MS, Lee KH, Kim BS, Do Yoo Y. 2011. Romo1 is a negative-feedback regulator of Myc. *Journal of cell science* **124**: 1911-1924.

Yuan J, Luo K, Zhang L, Cheville JC, Lou Z. 2010. USP10 regulates p53 localization and stability by deubiquitinating p53. *Cell* **140**: 384-396.
RAR activation 1.5 fold by WSB1

Ratio

-log (p-value)

-4 -3 -2 -1 0 1 2 3 4

- RAR activation
- RhoA Signaling
- Molecular Mechanisms of Cancer
- Acute Myeloid Leukemia Signaling
- BMP signaling pathway
- Ephrin Receptor signaling
- Signaling by Rho Family GTPases
- P38 MAPK signaling
- RhoGDI signaling
- Actin Nucleation by ARP-WASP complex
- Thrombin Signaling
- PPARo/PXR Activation
- Thrombin Signaling
- Ephrin B Signaling
- Axonal Guidance Signaling
- Hepatic Fibrosis / Hepatic Stellate Cell Activation

Kim et al., Supplemental Figure S1
## Top Bio Functions

### Diseases and Disorders

| Name                                | p-value           | # Molecules |
|-------------------------------------|-------------------|-------------|
| Cancer                              | 6.80E-10 - 8.22E-03 | 703         |
| Infectious Disease                  | 7.62E-08 - 4.42E-03 | 280         |
| Developmental Disorder              | 3.76E-07 - 5.70E-03 | 285         |
| Organismal Injury and Abnormalities | 2.94E-06 - 6.56E-03 | 332         |
| Reproductive System Disease         | 3.02E-05 - 6.22E-03 | 246         |

### Molecular and Cellular Functions

| Name                                      | p-value           | # Molecules |
|-------------------------------------------|-------------------|-------------|
| Gene Expression                           | 4.27E-12 - 5.32E-03 | 401         |
| Cellular Assembly and Organization        | 5.05E-11 - 6.04E-03 | 330         |
| Cellular Function and Maintenance         | 5.05E-11 - 6.38E-03 | 452         |
| Cellular Growth and Proliferation         | 9.76E-11 - 6.83E-03 | 551         |
| Cell Death and Survival                   | 1.60E-10 - 6.04E-03 | 545         |

### Physiological System Development and Function

| Name                                      | p-value           | # Molecules |
|-------------------------------------------|-------------------|-------------|
| Organismal Survival                       | 2.25E-09 - 3.99E-03 | 304         |
| Organismal Development                    | 1.21E-08 - 6.38E-03 | 398         |
| Organismal Functions                      | 1.22E-08 - 4.18E-03 | 54          |
| Tissue Morphology                         | 1.22E-08 - 6.34E-03 | 392         |
| Cardiovascular System Development and Function | 1.81E-07 - 6.33E-03 | 248         |

## Top Canonical Pathways

| Name                               | p-value           | Ratio |
|------------------------------------|-------------------|-------|
| RAR Activation                     | 2.89E-05          | 30/189 |
| RhoA Signaling                     | 6.48E-05          | 25/114 |
| Molecular Mechanisms of Cancer     | 5.12E-04          | 53/277 |
| Acute Myeloid Leukemia Signaling   | 1.22E-03          | 17/82  |
| BMP signaling pathway              | 1.82E-03          | 16/80  |

## Top Tox Functions

### Assays: Clinical Chemistry and Hematology

| Name                                      | p-value           | # Molecules |
|-------------------------------------------|-------------------|-------------|
| Increased Levels of Red Blood Cells       | 5.88E-03 - 5.88E-03 | 18          |
| Increased Levels of Hematocrit           | 5.89E-02 - 5.89E-02 | 15          |
| Increased Levels of Albumin              | 9.92E-02 - 9.92E-02 | 1           |
| Increased Levels of Alkaline Phosphatase  | 2.69E-01 - 1.00E00 | 7           |

### Cardiotoxicity

| Name                                      | p-value           | # Molecules |
|-------------------------------------------|-------------------|-------------|
| Cardiac Dysfunction                      | 5.73E-04 - 6.48E-01 | 18          |
| Cardiac Hypertrophy                      | 8.71E-04 - 3.00E-01 | 59          |
| Congenital Heart Anomaly                 | 2.68E-03 - 1.00E00 | 22          |
| Cardiac Fibrosis                         | 4.16E-03 - 5.45E-01 | 30          |
| Cardiac Arrhythmia                       | 9.83E-03 - 6.04E-01 | 23          |

### Hepatotoxicity

| Name                                      | p-value           | # Molecules |
|-------------------------------------------|-------------------|-------------|
| Liver Proliferation                       | 1.08E-02 - 3.75E-01 | 31          |
| Liver Necrosis/Cell Death                 | 1.34E-02 - 6.09E-01 | 30          |
| Liver Cirrhosis                          | 1.49E-02 - 2.69E-01 | 23          |
| Liver Cholestasis                        | 2.32E-02 - 5.19E-01 | 18          |
| Glutathione Depletion In Liver            | 4.18E-02 - 6.48E-01 | 6           |

### Nephrotoxicity

| Name                                      | p-value           | # Molecules |
|-------------------------------------------|-------------------|-------------|
| Renal Necrosis/Cell Death                 | 4.16E-03 - 5.28E-01 | 45          |
| Glomerular Injury                         | 1.49E-02 - 4.11E-01 | 16          |
| Kidney Failure                           | 3.45E-02 - 1.00E00 | 24          |
| Renal Damage                             | 5.15E-02 - 5.75E-01 | 31          |
| Renal Proliferation                      | 5.58E-02 - 4.85E-01 | 26          |
Kim et al., - Supplemental Figure S4

A

+ + + WSB1-myc HA-HIF-1α HA-VHL Vector
+ + + WSB1-myc HA-HIF-1α HA-VHL Vector
+ + + WSB1-myc HA-HIF-1α HA-VHL Vector

IP : HA

Myc (WSB1)
HA (pVHL)
HA (HIF-1α)

IP : Myc

pVHL
HA (HIF-1α)
Myc

Input (30%)

Myc
HA (pVHL)
HA (HIF-1α)

B

H522 H1299 H1640 H460 A549 BxPC3 Mia-Paca Pan02 04.03 ASPC1 MCF10A HT-29 HCC1937 HCC1806 MDA231

pVHL
HIF-1α
WSB1
β-actin

Lung Pancreatic Breast
Kim et al., - Supplemental Figure S5

A

**WSB1 shRNA (#1) vs WSB1 shRNA (#2)**

- **HIF-1α**
- **DAPI**
- **WSB1 shRNA-GFP**
- **Red + Green Merge**

B

| Gene          | Control shRNA | WSB1 shRNA (#2) |
|---------------|---------------|-----------------|
| HIF-1α        | **1.5**       | **1.5**         |
| VEGFA         | 1.0           | **1.5**         |
| ALDOC         | 1.0           | **1.5**         |
| CA9           | 1.0           | **1.5**         |
| SAP30         | 1.0           | **1.5**         |

* * * **p < 0.05***
Colon cancer (n=18):

- VEGFA: $P = 0.066$
- ALDOC: n.s.
- CA9: n.s.
- HK2: $P = 0.0235$
- MMP-9: $P = 0.0018$
- PDK1: n.s.

Urinary bladder cancer (n=13):

- VEGFA: $P = 0.004$
- ALDOC: n.e.
- CA9: n.s.
- HK2: n.s.
- MMP-9: $P = 0.0183$
- PDK1: $P = 0.0110$

Normalized target gene's expression values

Normalized WSB1's expression values

Kim et al., - Supplemental Figure S6
Ratio of invasion

Control shRNA
WSB1 shRNA

Cell number per field

Control shRNA
WSB1 shRNA

HIF-2α
pVHL
Myc (WSB1)
β-actin

Myc
WSB1-Myc
Control shRNA
WSB1 shRNA

Myc
WSB1-Myc
Control shRNA
WSB1 shRNA

Vector
WSB1
Control shRNA
WSB1 shRNA

Ratio of HIF-1α activity (Firefly / Renilla)

Vector
WSB1
ΔSOCS
WSB1:shRNA

Control shRNA
Myc
WSB1 shRNA

Control shRNA
Myc
WSB1 shRNA

Kim et al., Supplemental Figure S8
Kim et al., - Supplemental Figure S9

**Case 1**

| Control shRNA | Vector | 0 | 2 |
|---------------|--------|---|---|
| HIPK2 shRNA   | WSB1 (Wt) | 0 | 2 |
| WSB1 (Δ SOCS) | 0 | 2 |

**Case 2**

| Control shRNA | Vector | 0 | 2 |
|---------------|--------|---|---|
| HIPK2 shRNA   | WSB1 (Wt) | 0 | 2 |
| WSB1 (Δ SOCS) | 0 | 2 |

+ + WSB1 (Δ SOCS)-Myc
+ + WSB1 (Wt)-Myc

HIF-1α
pVHL
Myc
HIPK2
β-actin

(Days)

0
2

Case 1

Case 2

Kim et al., - Supplemental Figure S9
**A**

| shRNA    | DNA (WSB1) | # of Lung Metastasis |
|----------|------------|----------------------|
| Control  | Vector     |                      |
| WSB1     | Vector     |                      |
| WSB1     | Wt         |                      |

**B**

**C**

**D**
## Supplemental Table 1. The GEO Dataset.

| Cancer Type                              | Data set  | Platform | Series  | #samples |     |     |
|------------------------------------------|-----------|----------|---------|----------|-----|-----|
|                                           |           |          |         |          | Total | Metastasis |
| Melanoma                                 | GDS13966  | GPL96    | GSE840  | 83       | 50  |
| Prostate                                 | GDS2545   | GPL8300  | GSE6916 | 171      | 25  |
| Synchronous and metachronous liver       | GDS13501  | GPL570   | GSE10961| 18       | 18  |
| metastases from colorectal cancer        |           |          |         |          |     |     |
| Carcinoma in situ lesions of the urinary| GDS1479   | GPL96    | GSE3167 | 37       | 13  |
| bladder                                  |           |          |         |          |     |     |
| Breast                                   | GDS1306   | GPL96    | GSE5847 | 47       | 34  |
Supplemental Table 2. Differentially Expressed Meta_Related Genes by WSB1 Status in Never-Smoker Lung Adenocarcinoma. (Positively related)

| ID   | Genes in dataset | p-value (Wsb1 status) | Fold-Change (WSB1 High Expression vs WSB1 Low expression) |
|------|------------------|----------------------|---------------------------------------------------------|
| CXCR4 | CXCR4            | 9.29E-08             | 2.365                                                   |
| HGF   | HGF              | 6.65E-11             | 2.175                                                   |
| FABP5 | FABP5            | 3.01E-07             | 2.069                                                   |
| EGF   | EGF              | 2.84E-06             | 2.026                                                   |
| ANGPT2| ANGPT2           | 2.42E-07             | 1.917                                                   |
| PPM1D | PPM1D            | 9.39E-09             | 1.875                                                   |
| ZAP70 | ZAP70            | 5.16E-10             | 1.844                                                   |
| MMP9  | MMP9             | 3.54E-05             | 1.84                                                    |
| CA4   | CA4              | 2.49E-06             | 1.783                                                   |
| VEGFA | VEGFA            | 1.14E-05             | 1.749                                                   |
| TACSTD1 | EPCAM          | 2.53E-06             | 1.702                                                   |
| NUAK1 | NUAK1            | 1.26E-07             | 1.693                                                   |
| LGALS3| LGALS3           | 3.69E-10             | 1.686                                                   |
| HK2   | HK2              | 3.52E-06             | 1.683                                                   |
| SLC38A6 | SLC38A6        | 2.54E-09             | 1.667                                                   |
| NT5E  | NT5E             | 4.89E-05             | 1.651                                                   |
| HTATIP2 | HTATIP2        | 3.40E-05             | 1.639                                                   |
| OLFML3| OLFML3           | 6.40E-07             | 1.617                                                   |
| ANK3  | ANK3             | 1.29E-07             | 1.609                                                   |
| SP4   | SP4              | 3.76E-09             | 1.599                                                   |
| CAPN2 | CAPN2            | 6.11E-08             | 1.595                                                   |
| SLC16A3| SLC16A3          | 8.32E-06             | 1.591                                                   |
| DLG7  | DLGAP5           | 0.0064403            | 1.586                                                   |
| CYP1B1| CYP1B1           | 6.01E-07             | 1.58                                                    |
| ESR1  | ESR1             | 0.0007115            | 1.574                                                   |
| TUBE1 | TUBE1            | 2.74E-07             | 1.572                                                   |
| NDRG1 | NDRG1            | 2.12E-05             | 1.565                                                   |
| MET   | MET              | 0.0002945            | 1.561                                                   |
| MMP2  | MMP2             | 6.54E-07             | 1.556                                                   |
| TGFA  | TGFA             | 0.0001149            | 1.552                                                   |
| TUBD1 | TUBD1            | 5.82E-08             | 1.55                                                    |
| CAT   | CAT              | 2.38E-08             | 1.545                                                   |
| AKR1C3 | AKR1C3          | 0.0002158            | 1.53                                                    |
| APC   | APC              | 1.52E-07             | 1.52                                                    |
| CFLAR | CFLAR            | 8.53E-11             | 1.519                                                   |
| SELE  | SELE             | 0.0003739            | 1.512                                                   |
| TUBB2C| TUBB4B           | 2.89E-07             | 1.509                                                   |
| ANGPTL4 | ANGPTL4       | 2.33E-05             | 1.505                                                   |
Supplemental Table 2. Differentially Expressed Meta_Related Genes by WSB1 Status in Never-Smoker Lung Adenocarcinoma. (Negatively related)

| ID  | Genes in dataset | p-value (Wsb1 status) | Fold-Change (WSB1 High Expression vs WSB1 Low expression) |
|-----|------------------|-----------------------|----------------------------------------------------------|
| NF2 | NF2              | 8.12E-11              | -2.454                                                   |
| RASSF3 | RASSF3      | 1.15E-09              | -2.291                                                   |
| TP73L | TP63        | 0.0133901             | -1.868                                                   |
| TP53 | TP53           | 1.86E-05              | -1.817                                                   |
| SDC1 | SDC1           | 3.37E-07              | -1.792                                                   |
| KISS1 | KISS1        | 0.0031178             | -1.732                                                   |
| WWOX | WWOX           | 6.83E-11              | -1.714                                                   |
| NLRP1 | NLRP1        | 3.05E-05              | -1.669                                                   |
| SCUBE2 | SCUBE2       | 0.0156027             | -1.641                                                   |
| DFB  | DFB            | 4.22E-07              | -1.637                                                   |
| REV3L | REV3L        | 3.55E-05              | -1.634                                                   |
| LGR4 | LGR4           | 0.007748              | -1.581                                                   |
| IL1RL1 | IL1RL1     | 0.0191785             | -1.547                                                   |
| PPARD | PPARD        | 5.90E-05              | -1.53                                                    |
| STAB2 | STAB2        | 0.0215461             | -1.53                                                    |
| GREM2 | GREM2        | 0.0113608             | -1.519                                                   |