Titles and legends to supplementary figures:

Figure S1. MS results of identified ISM binding partners in plasma membrane and mitochondria:

(**a-b**) Identified ISM's binding partners in plasma membrane fraction. (**a**) MS result of clathrin heavy chain 1 (CHC1). (**b**) MS result of glucose-regulated protein of 78 kDa (GRP78). (**c-g**) Identified ISM's binding partners in mitochondria. (**c**) MS result of clathrin heavy chain 1 (CHC1). (**d**) MS result of glucose-regulated protein of 78 kDa (GRP78). (**e**) MS result of ISM. (f) MS result of ADP/ATP carrier 2 (AAC2). (**g**) MS result of ADP/ATP carrier 3 (AAC3). Bold red sequences represent the matched peptides by MALDI-TOF-TOF MS. Protein scores greater than 64 are significant ($p<0.05$).

Figure S2. ISM inhibits angiogenesis through GRP78. (**a**) Transient transfection of two different siRNAs effectively knocked down GRP78 expression in HUVECs. Equal amount of scramble siRNA was transfected as a control. (**b**) Knockdown of GRP78 expression by siRNAs diminished ISM-mediated EC adhesion. *$P<0.05$, n=3. Error bars denote SEM. (**c-d**) Knockdown of GRP78 expression by siRNAs compromised the anti-tube formation action of ISM. *$P<0.05$, n=3. Error bars denote SEM. (**e**) Knockdown of GRP78 expression by siRNAs reduced ISM-induced EC apoptosis. *$P<0.05$, n=3. Error bars denote SEM.

Figure S3. GRP78 mediates ISM internalization. (**a**) Anti-GRP78 antibody

reduced ISM internalization into HUVECs in a dose-dependent manner. (**b**) Internalized ISM-GRP78 complex mainly associated with CHC but not caveolin. ISM pre-treated HUVECs were washed to remove cell surface associated ISM and lysed in 1% Triton X-100 buffer. Triton-insoluble and -soluble fractions of HUVEC plasma membrane lysates were prepared by density centrifugation. Immunoblotting with antibodies against ISM, αvβ5 integrin subunit β5 and GRP78 was used to analyze each fraction. Caveolin-1 and clathrin heavy chain (CHC) were used as markers for lipid-raft and non lipid-raft fraction. (**c**) Overexpression of GRP78 but not αvβ5 integrin increased ISM internalization in LS174T cells.

Figure S4. ISM selectively induces apoptosis in cells that express high level cell-surface GRP78 such as invasive cancer cells and activated ECs. (**a**) GRP78 level in the plasma membrane fraction of NIH3T3, SWISS3T3, HUVEC, HEK293T, B16F10, 4T1, LS174T, LS-LM6 and 786-O cells. Equal amount of plasma membrane proteins were loaded as shown in the coomassie blue stained gel. (**b-j**) ISM only induced significant apoptosis in cells exhibiting high level cell-surface GRP78. B16F10 (mouse melanoma), 4T1 (mouse breast carcinoma), 786-O (human renal carcinoma), LS-LM6 and LS174T (human colon cancer). ***P*<0.01, n=3. Error bars denote SEM.

Figure S5. Overexpression of GRP78 or αvβ5 integrin conferred the pro-apoptotic function of ISM in LS174T cells. (**a**) Increasing αvβ5 integrin

expression level dose-dependently enhanced the pro-apoptotic effect of ISM on LS174T cells. (**b**) Simultaneous overexpression of GRP78 and αvβ5 integrin generated more potent apoptotic response to ISM than overexpression of individual receptor in LS174T cells (compare to Fig. 3d and Fig. S5a respectively).

Figure S6. ISM interacts with AAC2 in mitochondria and blocks ADP import from cytoplasm into mitochondria. (**a**) ISM-induced morphology change of HUVECs is dependent on caspase activity. HUVECs were either treated by rISM or rISM plus Z-VAD-fmk as the pan-caspase inhibitor for 24 h. Mitochondria were labeled by red MitoTracker. Internalized rISM was detected by IF using antibody against his-tag. Nuclei were stained by DAPI. (**b**) Internalized ISM-GFP co-localized with AAC2. ISM-GFP expression plasmid was transiently transfected into HEK293T cells. Condition media was collected and applied to mCherry-AAC2 transfected HEK293T cells. ISM (green) co-localized with AAC2 (red) in mCherry-AAC2 expressing cells. Nuclei were stained with DAPI (blue). Quantitative measurement of Pearson's correlation coefficient (*Rp*) between red and green fluorescent signals of the arrow-labeled cell was indicated in the far-right. (**c**) rISM treatment increased ADP level in cytosolic fraction of HUVECs independent of caspase activity. Z-VAD-fmk was used as pan-caspase inhibitor. ***P*<0.01, n=3. Error bars denote SEM. (**d**) rISM treatment decreased ADP level in mitochondrial fraction of HUVECs independent of caspase activity. ***P*<0.01, n=3. Error bars denote

SEM. (**e**) rISM treatment increased ADP concentration in whole cell lysates of HUVECs independent of caspase activity. *P<0.05, n=3. Error bars denote SEM.

Figure S7. GRP78 and αvβ5 integrin present distinct distribution patterns in both B16F10 and 4T1 tumors. Paraffin sections of B16F10 and 4T1 tumors from rISM-treated and control groups were double-stained for both GRP78 and αvβ5 integrin through IF using anti-GRP78 (red) and anti-αvβ5 integrin (green). Nuclei were counter stained by DAPI (blue). Representative photos are shown. Quantitative measurements of Pearson's correlation coefficient (*Rp*) between red and green fluorescent labeled channels were indicated in the far-right.

Figure S8. Systemically delivered rISM suppresses B16 melanoma growth in mice by inducing apoptosis of both cancer cells and cancer ECs. (a-d), ISM inhibits B16 melanoma growth in mice when delivered systematically. (**a**) B16F10 tumor growth curve in mice. X-axis represents the days after inoculation of 5×10^5 tumor cells. Groups consisted of control mice receiving no treatment or 250 μg rISM through tail vein injection every other day from day 0 (date of inoculation) to 14. N=5. (**b**) Tumor weight at the end of the experiment (day 14). (**c**) Dissected tumors at the end of experiment. (**d**) rISM treated tumors showed a reduced vascularization compared to untreated control. (**e**) rISM suppressed tumor angiogenesis, proliferation and induced

apoptosis in B16F10 tumor. Paraffin sections of B16F10 tumors from control and treated groups with rISM were probed for microvascular density (MVD), tumor cell proliferation and apoptosis through IF using anti-CD31, anti-PCNA and TUNEL staining respectively. (**f**) Quantification of MVD, cell proliferation and apoptosis. Plots represent the mean of 3 fields per section, 3 sections per tumor and 2 tumors per group. $^{**}P<0.01$. Error bars denote SEM. (**g**) ISM induces apoptosis of both cancer cells and cancer ECs in B16 melanoma. Double IF using anti-CD31 (red) and TUNEL (green) is shown. Nuclei were counter stained by DAPI (blue). Representative photos are shown. Apoptotic EC is indicated by white arrow.

Supplementary Materials and Methods

DNA constructs

The human AAC2 cDNA was amplified by primer pair (5' TCTCGAGATGACAGATGCCGCTGTG3' and 5' CTGGTACCGTTATGTGTACTTCTTGATTTC3') and cloned into pXJ40_mCherry to obtain pXJ40_mCherry-AAC2.

Syngeneic tumorigenesis assay

B16F10 cells (5×10^5) were injected subcutaneously into the dorsal flank of 8-week old female C57BL/6J mice. Two groups of mice (n=5/group) received either PBS or 250 μg rISM by tail vein injection every other day from day 0 to the end point (day 14). Tumors were measured and processed as described.[1]

Tube formation assay

EC tube formation assay was performed using *in vitro* angiogenesis assay kit (Millipore, Billerica, MA, USA) according to the manufacturers' instruction. The matrigel was plated into a μ-Slide Angiogenesis chamber (ibidi, Martinsried, Germany) and kept at 37℃ for 1 h to solidify. For studying the contribution of GRP78 to the anti-tube formation activity of ISM, HUVECs were pre-transfected by siRNAs of GRP78 for 48h. HUVECs transfected with scramble siRNA served as control. Then 1×10^4 cells per sample in 50 μl basal medium were treated with 1μM rISM for 30 min and plated onto the polymerized Matrigel and incubated at 37°C for 6–8 h before documenting the tubular structure formation using Zeiss Axiovert 200 inverted light microscope (Carl Zeiss South East Asia, Singapore). Capillary length from representative fields was quantified by ImageJ (National Institutes of Health, USA).

Apoptosis assay

To investigate the contribution of GRP78 to ISM-induced EC apoptosis, HUVECs were pre-transfected by GRP78 siRNAs for 48 h. Control HUVECs

were transfected by scramble siRNA. Cells (2×10^4) were then seeded into 96-well plate. After starving in 2% FBS basal medium for 3 h, HUVECs were treated with 1 μM rISM and 15 ng/ml VEGF for 24 h. Apoptosis was detected by a Cell Death ELISA kit (Roche, Roche Diagnostics Asia Pacific, Singapore)

Cell attachment assay

Ninety-six well plates were coated with 1 μM rISM at 4°C overnight. Nonspecific binding sites were blocked with 1% BSA for 2 h at 37°C. HUVECs were pre-transfected by GRP78 siRNAs or scramble control siRNA for 48 h before they were plated into each well (2×10^4 cells/well) and allowed to attach for 1 h at 37°C. Attached cells were fixed by 10% formalin and stained with 0.2% crystal violet. Absorbed crystal violet was extracted by 10% acetic acid and quantified by measuring the absorbance of eluted dye at 595 nm with a microplate reader (Bio-Rad, Hercules, CA, USA).

Internalized ISM triton partitioning

Triton-insoluble and -soluble fractions of HUVEC lysate were prepared as previously described[2]. HUVECs were treated with 1 μM rISM for 24 h. After thoroughly washed by acidic PBS (pH3.5) to remove cell surface associated ISM, the cells were lysed in 1 ml of 1% Triton X-100 in 2-(N-morpholino)ethanesulfonic acid (MES)-buffered saline (25 mM MES, 0.15 M NaCl, 1×protease inhibitor cocktail, pH 6.5) (Sigma, St. Louis, MO, USA) for

30 min on ice. Cell extracts were homogenized by a tight-fitting Dounce homogenizer (Wheaton, Millville, NJ, USA) and adjusted to a final density of 40% by adding OptiPrep density gradient Medium (Sigma). Samples were transferred into a centrifuge tube and overlaid with discontinuous 30% and 5% OptiPrep density gradient media. Samples were then centrifuged at 39,000 rpm for 18 h. Fractions were collected and analyzed by WB with antibodies against ISM (his-probe), integrin β5 subunit and GRP78. Caveolin-1 and clathrin heavy chain (CHC) were used as markers for lipid-raft and non lipid-raft fraction.

ADP colorimetric assay

The ADP concentrations in whole cell lysate, mitochondrial and cytosolic (without mitochondria) fractions in HUVECs with indicated treatment of 1μM rISM or 10 μM pan-caspase inhibitor - Z-VAD-fmk (Millipore, Billerica, MA, USA) for 3 h were analyzed using the ADP colorimetric assay kit (BioVision, Milpitas, CA, USA).

Determination of ISM-treated HUVECs morphology under caspase inhibitor

HUVECs were starved for 3 h in 2% FBS media and then incubated with 2% FBS medium containing 15 ng/ml VEGF. HUVECs were either received no additional treatment as the control or treated by 1μM rISM with or without 10

μM pan-caspase inhibitor - Z-VAD-fmk for 24 h. Cells were then incubated with MitoTracker for 30 min and washed by acidic PBS (pH 3.5) to remove surface bound rISM. Internalized rISM was detected by IF staining using anti-his antibody. Nuclei were stained by DAPI. Images were collected by Zeiss LSM-510Meta confocal microscope.

RNAi gene knockdown

To knockdown human GRP78, two synthetic siRNA were used (Integrated DNA Technologies, Singapore): siRNA1-GRP78 (5'-GGAGCGCAUUGAUACUAGAUU-3')[3] and siRNA2-GRP78 (5'-AGACGCUGGAACUAUUGCUUU-3')[4]. A random scramble siRNA (5'-AAUUCUCCGAACGUGUCACGUUU-3') was used as the control[3].

References

1. Kumar S, Sharghi-Namini S, Rao N, Ge RW. ADAMTS5 Functions as an Anti-Angiogenic and Anti-Tumorigenic Protein Independent of Its Proteoglycanase Activity. *Am J Pathol* 2012; **181**(3)**:** 1056-1068.
2. Wickstrom SA, Alitalo K, Keski-Oja J. Endostatin associates with lipid rafts and induces reorganization of the actin cytoskeleton via down-regulation of RhoA activity. *J Biol Chem* 2003; **278**(39)**:** 37895-901.
3. Tsutsumi S, Namba T, Tanaka KI, Arai Y, Ishihara T, Aburaya M *et al.* Celecoxib upregulates endoplasmic reticulum chaperones that inhibit celecoxib-induced apoptosis in human gastric cells. *Oncogene* 2006; **25**(7)**:** 1018-29.
4. Su R, Li Z, Li H, Song H, Bao C, Wei J *et al.* Grp78 promotes the invasion of hepatocellular carcinoma. *BMC cancer* 2010; **10:** 20.

Fig. S1

a

Protein View

Match to: **gi|4758012** Score: **205** Expect: **4.1e-016**
clathrin heavy chain 1 [Homo sapiens]

Matched peptides shown in **Bold Red**

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  51 VIIDMNDPSN PIRRPISADS AIMNPASKVI ALKAGKTLQI FNIEMKSKMK
 101 AHTMTDDVTF WKWISLNTVA LVTDNAVYHW SMEGESQPVK MFDRHSSLAG
 151 CQIINYRTDA KQKWLLLTGI SAQQNRVVGA MQLYSVDRKV SQPIEGHAAS
 201 FAQFKMEGNA EESTLFCFAV RQQAGGKLHI IEVGTPPTGN QFFPKKAVDV
 251 FFPPEAQNDF PVAMQISEKH DVVFLITKYG YIHLYDLETG TCIYMNRISG
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 351 MAVRNNLAGA EELFARKFNA LRAQGNYSEA AKVAANAPKQ ILRTPQTIRR
 401 FQSVPAQPGQ TSPLLQYTSI LLDQGQLNKV ESLELCRPVL QQGRHQLLEK
 451 WLKEDKLECS EELGDLVKSV DPTLALSVYL RANVPNKVIQ CFAETGQVQK
 501 IVLYAKKVGY TPDWIFLLRN VMRISPDQGQ QFAQMLVQDE EPLADITQIV
 551 DVFMEYNLIQ QCTAFLLDAL KNNRPSEGPL QTRLLEMNLM HAPQVADAIL
 601 GNQMFTHYDR AHIAQLCEKA GLLQRALEHF TDLYDIKRAV VHTHLLNPEW
 651 LVNYFGSLSV EDSLECLRAM LSANIRQNLQ ICVQVASKYH EQLSTQSLIE
 701 LFESFKSFEG LFYFLGSIVN FSQDPDVHFK YIQAACKTGQ IKEVCRICRE
 751 SNCYDPERVK NFLKEAKLTD QLPLIIVCDR FDFVHDLVLY LYRNNLQKYI
 801 EIYVQKVNPS RLPVVIGGLL DVDCSEDVIK NLILVVRGQF STDELVAEVE
 851 KRNRLKLLLP WLEARIHEGC EEPATNNALA KIYIDSNNNP ERFLRENPYY
 901 DSRVVGKYCE KRDFHLACVA YERGQCDLEL INVCNENSLF KSLSRYLVRR
 951 KDPKLWSSVL LESNPYRRPL IDQVVQTALS ETQDPEEVSV TVKAFHTADL
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1051 DAPDIANIAI SNELFEEAFA IFRKFDVNTS AVQVLIEHIG NLDRAYEFAE
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1201 VGDRCYDEKM YDAAKLLYNN VSNFGRLAST LVHLGEYQAA VDGARKANST
1251 RTWKEVCFAC VDGKEFRLAQ MCGLHIVVHA DELEELINYY QDRGYFEELI
1301 TMLEAAIGLE RAHMGMFTEL AILYSKFKPQ KMHEHLELFW SRVNIPKVLR
1351 AAEQAHLWAE LVFLYDKYEE YDNAIITMMN HPTDAWKEQQ FKDIITKVAN
1401 VELYYRAIQF YLEFKPLLLN DLLMVLSPRL DHTRAVNYFS KVKQLPLVKP
1451 YLRSVQMHRN KSVNESLNNL FITEEDYQAL RTSIDAYDNF DNISLAQRLE
1501 KHELIEFKRI AAYLFKGNNR WKQSVELCKK DSLYKDAMQY ASSKHDTELA
1551 KELLQWFLQE KERECFGACL FTCYDLLNKD VVLETANRHH IMDFAMPYFI
1601 QVMKEYLTKV DKLDASESLR KSEEQATETQ PIVYQQPQLM LTAGPSVAVP
1651 PQAPFGYGYT APPYQQPQPG FGYSM
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b

Protein View

Match to: **gi|16507237** Score: **353** Expect: **6.5e-031**
heat shock 70kDa protein 5 [Homo sapiens]

Matched peptides shown in **Bold Red**

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   1 MKLSLVAAML LLLSAARAEE EDKKEDVGTV VGIDLGTTYS CVGVFKNGRV
  51 EIIANDQGNR ITPSYVAFTP EGERLIGDAA KNQLTSNPEN TVFDAKRLIG
 101 RTWNDPSVQQ DIKFLPFKVV EKKTKPYIQV DIGGGQTKTF APEEISAMVL
 151 TKMKETAEAY LGKKVTHAVV TVPAYFNDAQ RQATKDAGTI AGLNVMRIIN
 201 EPTAAAIAYG LDKRGEGEKN ILVFDLGGGTF DVSLLTIDNG VFEVVATNGD
 251 THLGGEDFDQ RVMEHFIKLY KKKTGKDVRK DNRAVQKLRR EVEKAKRALS
 301 SQHQARIEIE SFYEGEDFSE TLTRAKFEEL NMDLFRSTMK PVQKVLEDSD
 351 LNKSDIDEIV LVGGSTRIPK IQQLVKEFFN GKEPSRGINP DEAVAYGAAV
 401 QAGVLSGDQD TGDLVLLDVC PLTLGIETVG GVMTKLIPRN TVVPTKKSQI
 451 FSTASDNQPT VTIRVYEGER PLTKDNHLLG TFDLTGIPPA PRGVPQIEVT
 501 FEIDVNGILR VTAEDKGTGN KNKITITNDQ NRLTPEEIER MVNDAEKFAE
 551 EDKKLKERID TRNELESYAY SLKNQIGDKE KLGGKLSSED KETMEKAVEE
 601 KIEWLESHQD ADIEDFKAKK KELEEIVQPI ISKLYGSAGP PPTGEEDTAE
 651 KDEL
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c

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 301 ETIFVTAPHE ATAGIIGVNR KGQVLSVCVE EENIIPYITN VLQNPDLALR
 351 MAVRNNLAGA EELFARKFNA LRAQGNYSEA AKVAANAPKQ ILRTPETIRR
 401 FQSVPAQPGQ TSPLLQYTSI LLDQGQLNKV ESLELCRPVL QQGRHQLLEK
 451 WLKEDKLECS EELGDLVKSV DPTLALSVYL RANVPNKVIQ CFAETGQVQK
 501 IVLYAKKVGY TPDWIFLLRN VMRISPDQGQ QFAQMLVQDE EPLADITQIV
 551 DVFMEYNLIQ QCTAFLLDAL KNNRPSEGPL QTRLLEMNLM HAPQVADAIL
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 751 SNCYDPERVK NFLKEAKLTD QLPLIIVCDR FDFVHDLVLY LYRNNLQKYI
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1301 TMLEAAIGLE RAHMGMFTEL AILYSKFKPQ KMHEHLELFW SRVNIPKVLR
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1601 QVMKEYLTKV DKLDASESLR KSEEQATETQ PIVYQQPQLM LTAGPSVAVP
1651 PQAPFGYGYT APPYQQPQPG FGYSM
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d

Protein View

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78 kDa glucose-regulated protein [Homo sapiens]

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 501 FEIDVNGILR VTAEDKGTGN KNKITITNDQ NRLTPEEIER MVNDAEKFAE
 551 EDKKLKERID TRNELESYAY SLKNQIGDKE KLGGKLSSED KETMEKAVEE
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e

Protein View

Match to: **gi|187608602** Score: **491** Expect: **9.2e-043**
isthmin-1 precursor [Mus musculus]

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 301 YNNKVINDLP SCPCSYPTEV AYSTADIFDR IKKKDFRWKD ASGPKEKLEI
 351 YKPTARYCIR SMLSLESTTL AAQHCCYGDN MQLITNGKGA GTPNLISTEF
 401 SAELNYKVDV LEWIICKGDW SKYNEARPPN NGQKCTESPS DEDYIRQFQE
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f

Protein View

Match to: **gi|156071459** Score: **96** Expect: **5.3e-005**
ADP/ATP translocase 2 [Homo sapiens]

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  51 YKGIIDCVVR IPKEQGVLSF WRGNLANVIR YFPTQALNFA FKDKYKQIFL
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 201 MLPDPKNTHI VISWMIAQTV TAVAGLVSYP FDTVRRRMMM QSGRKGTDIM
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g

Protein View

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 151 EREFRGLGDC LVKITKSDGI RGLYQGFSVS VQGIIIYRAA YFGVYDTAKG
 201 MLPDPKNTHI VVSWMIAQTV TAVAGVVSYP FDTVRRRMMM QSGRKGADIM
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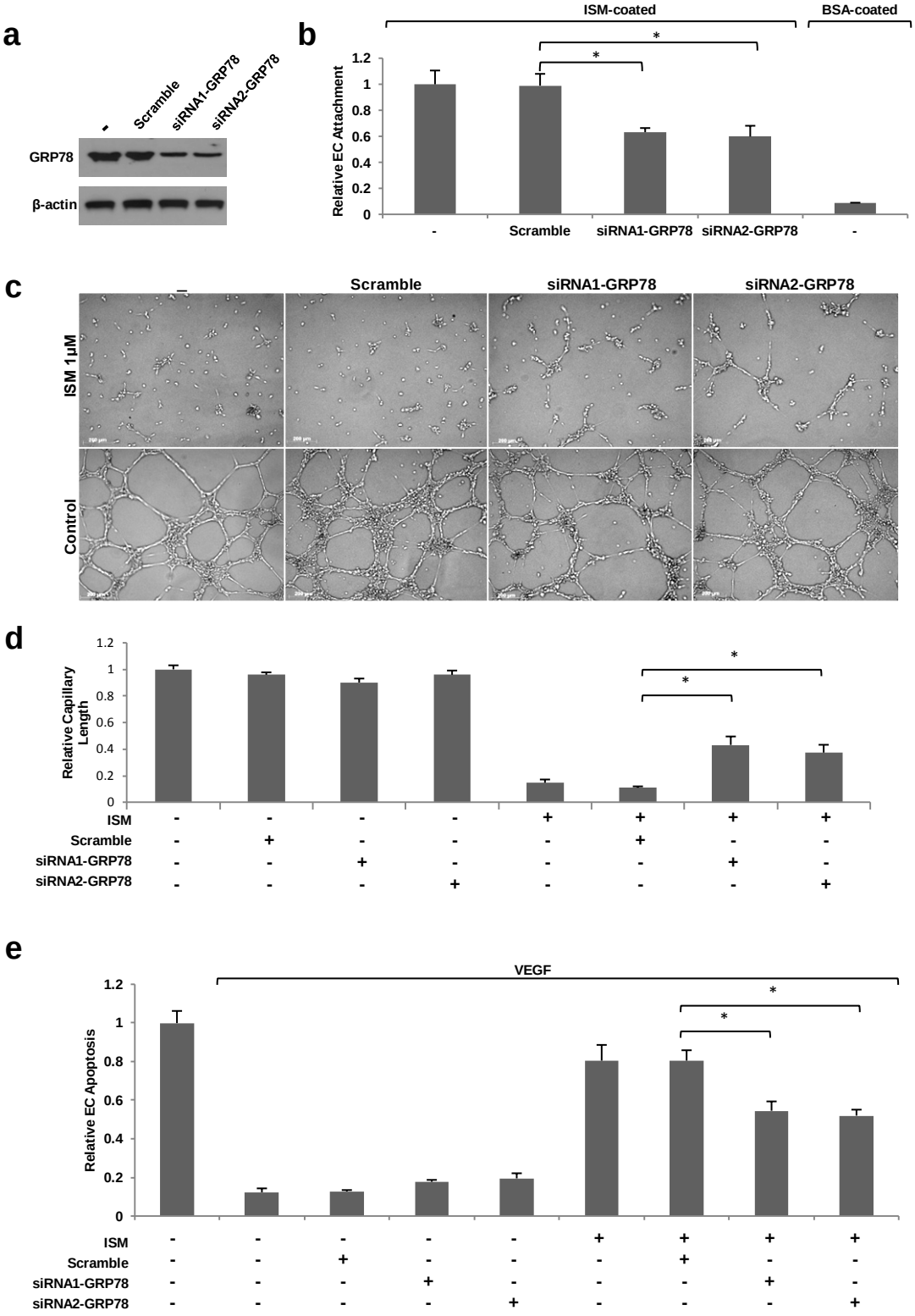
Fig. S2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siRNA2-GRP78
GRP78
β-actin
b
ISM-coated
BSA-coated
Relative EC Attachment
1.2
1
0.8
0.6
0.4
0.2
0
-
Scramble
siRNA1-GRP78
siRNA2-GRP78
-
c
-
Scramble
siRNA1-GRP78
siRNA2-GRP78
ISM 1μM
Control
d
Relative Capillary Length
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1
0.8
0.6
0.4
0.2
0
ISM
Scramble
siRNA1-GRP78
siRNA2-GRP78
e
VEGF
Relative EC Apoptosis
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0.6
0.4
0.2
0
ISM
Scramble
siRNA1-GRP78
siRNA2-GRP78

Fig. S3

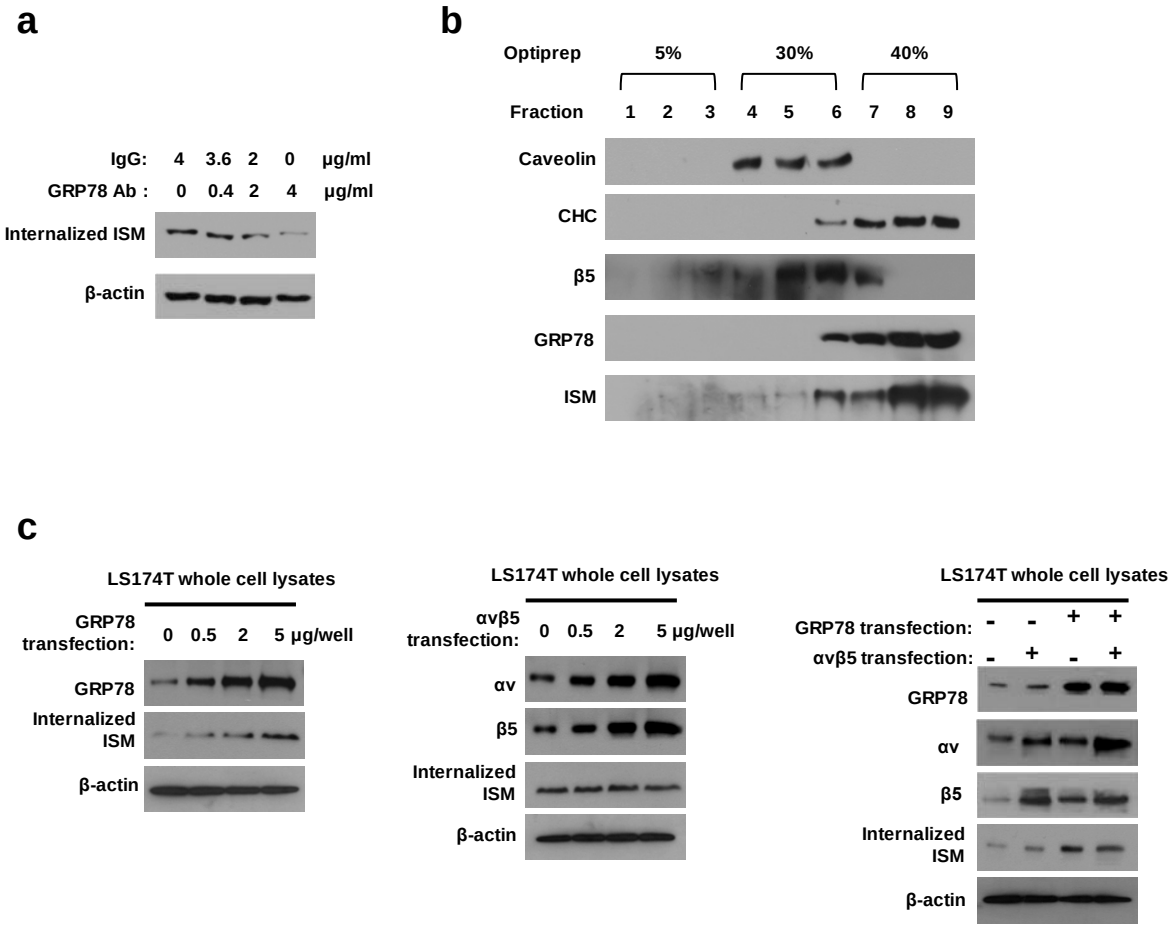

a
IgG: 4 3.6 2 0 μg/ml
GRP78 Ab : 0 0.4 2 4 μg/ml
Internalized ISM
β-actin
b
Optiprep
5%
30%
40%
Fraction 1 2 3 4 5 6 7 8 9
Caveolin
CHC
β5
GRP78
ISM
c
LS174T whole cell lysates
GRP78 transfection: 0 0.5 2 5 μg/well
GRP78
Internalized ISM
β-actin
LS174T whole cell lysates
αvβ5 transfection: 0 0.5 2 5 μg/well
αv
β5
Internalized ISM
β-actin
LS174T whole cell lysates
GRP78 transfection: - - + +
αvβ5 transfection: - + - +
GRP78
αv
β5
Internalized ISM
β-actin

Fig. S4

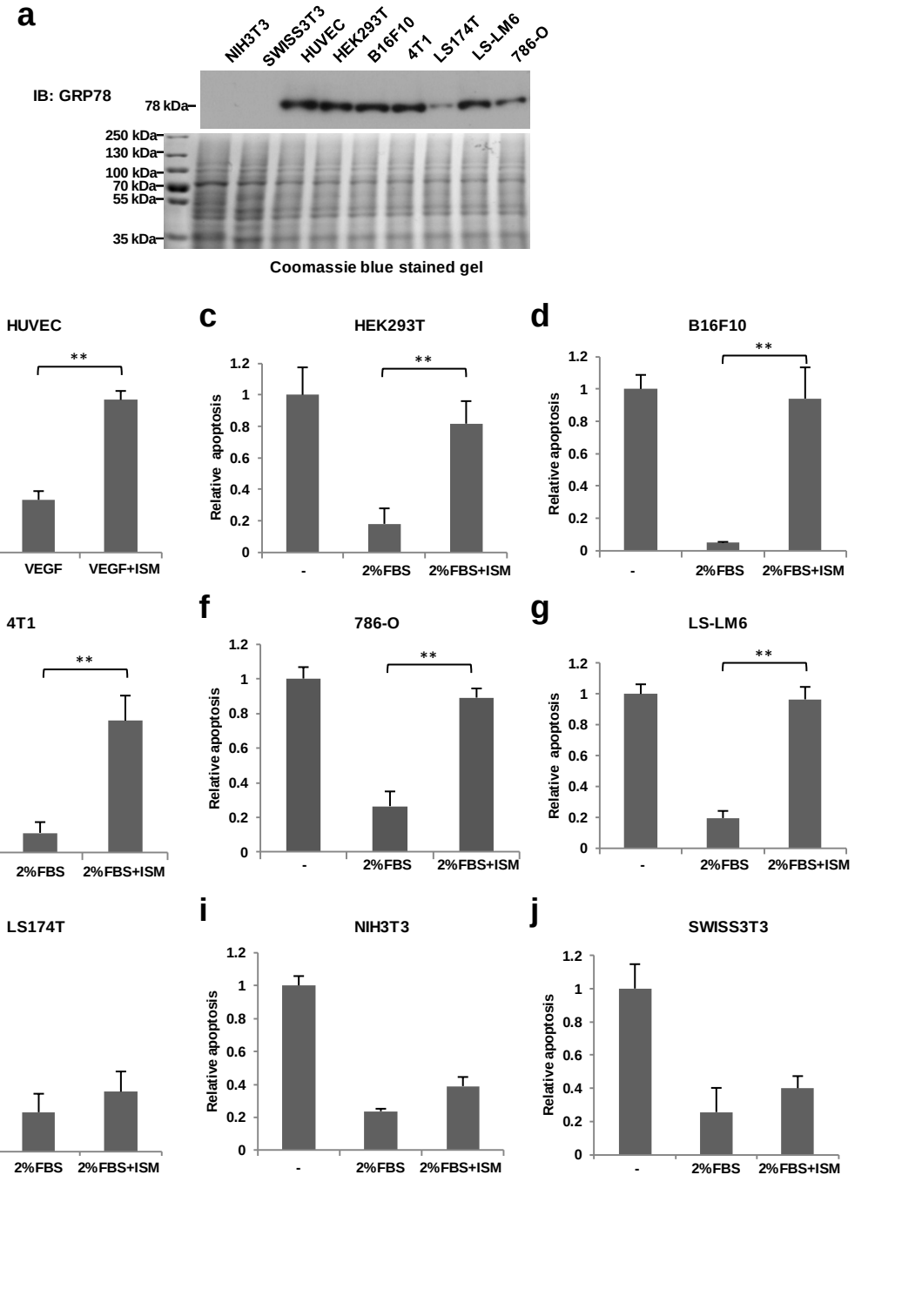

a
NIH3T3
SWISS3T3
HUVEC
HEK293T
B16F10
4T1
LS174T
LS-LM6
786-O
IB: GRP78
78 kDa
250 kDa
130 kDa
100 kDa
70 kDa
55 kDa
35 kDa
Coomassie blue stained gel
b
HUVEC
c
HEK293T
d
B16F10
e
4T1
f
786-O
g
LS-LM6
h
LS174T
i
NIH3T3
j
SWISS3T3
Relative apoptosis
**
-
VEGF
VEGF+ISM
2%FBS
2%FBS+ISM

Fig. S5

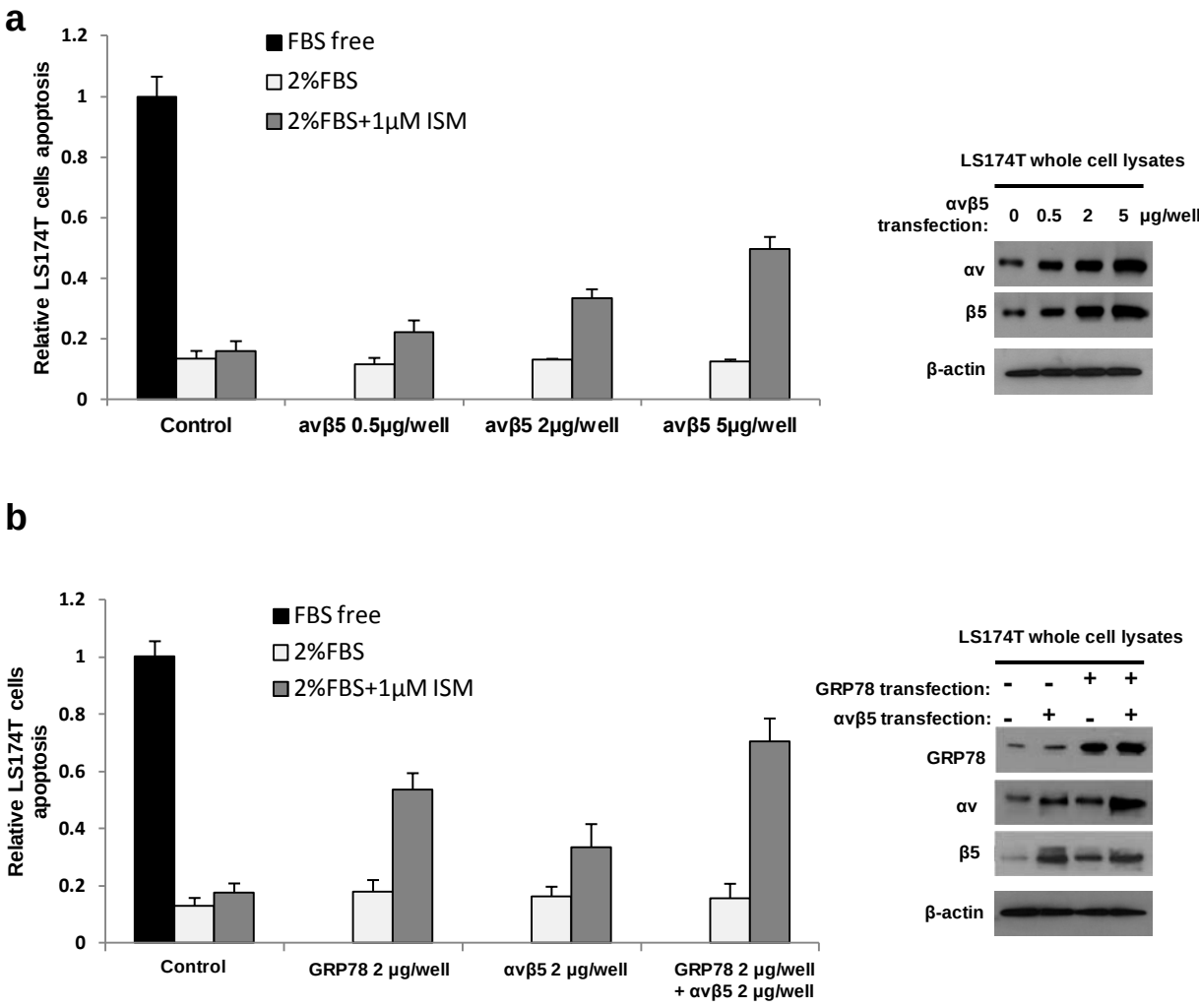

a
Relative LS174T cells apoptosis
1.2
1
0.8
0.6
0.4
0.2
0
FBS free
2%FBS
2%FBS+1μM ISM
Control
avβ5 0.5μg/well
avβ5 2μg/well
avβ5 5μg/well
LS174T whole cell lysates
αvβ5 transfection:
0 0.5 2 5 μg/well
αv
β5
β-actin
b
Relative LS174T cells apoptosis
1.2
1
0.8
0.6
0.4
0.2
0
FBS free
2%FBS
2%FBS+1μM ISM
Control
GRP78 2 μg/well
αvβ5 2 μg/well
GRP78 2 μg/well + αvβ5 2 μg/well
LS174T whole cell lysates
GRP78 transfection: - - + +
αvβ5 transfection: - + - +
GRP78
αv
β5
β-actin

Fig. S6

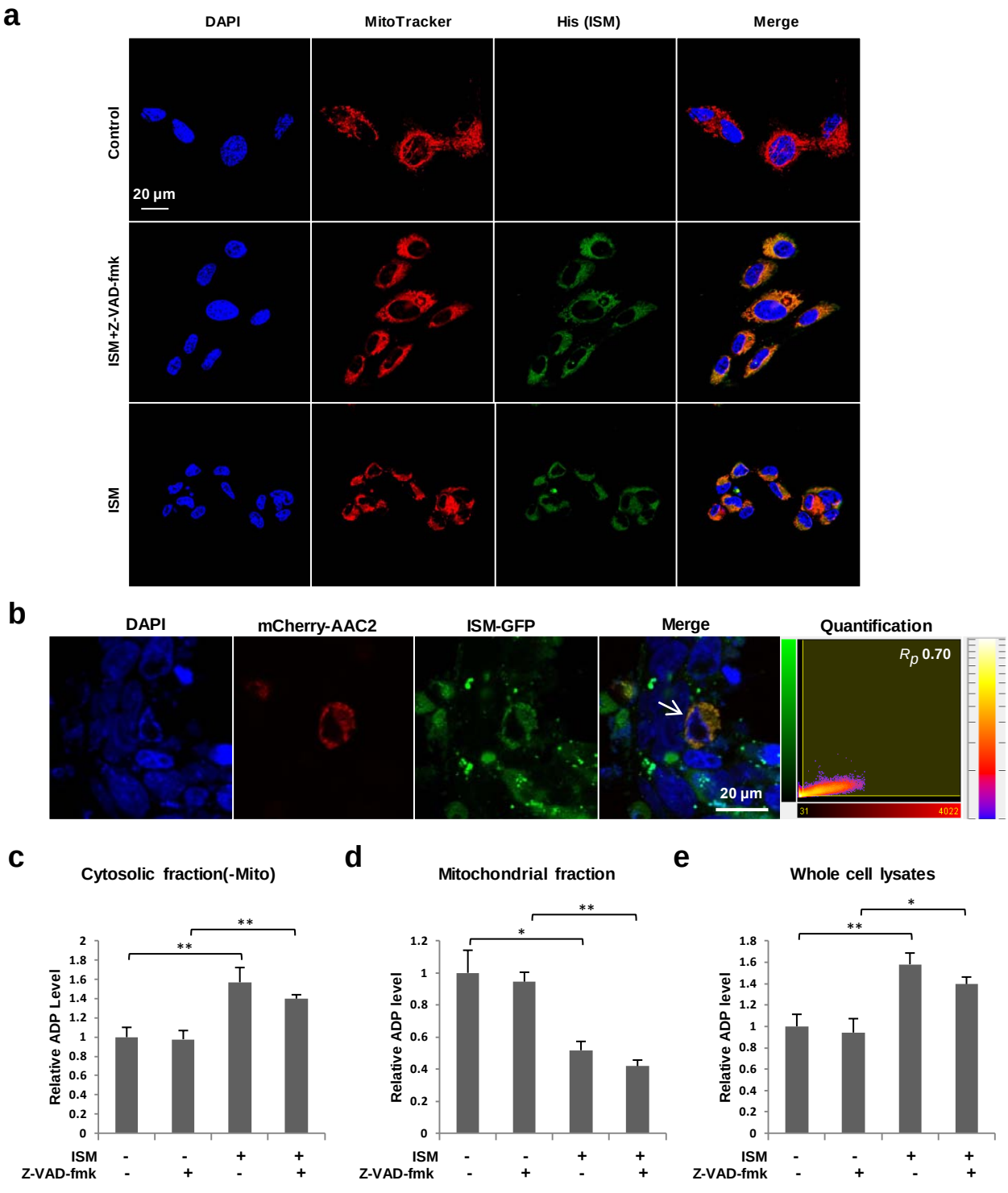

a
DAPI
MitoTracker
His (ISM)
Merge
Control
ISM+Z-VAD-fmk
ISM
20 μm
b
DAPI
mCherry-AAC2
ISM-GFP
Merge
Quantification
R_p 0.70
20 μm
31
4022
c
Cytosolic fraction(-Mito)
Relative ADP Level
d
Mitochondrial fraction
Relative ADP level
e
Whole cell lysates
Relative ADP level
ISM
Z-VAD-fmk

Fig. S7

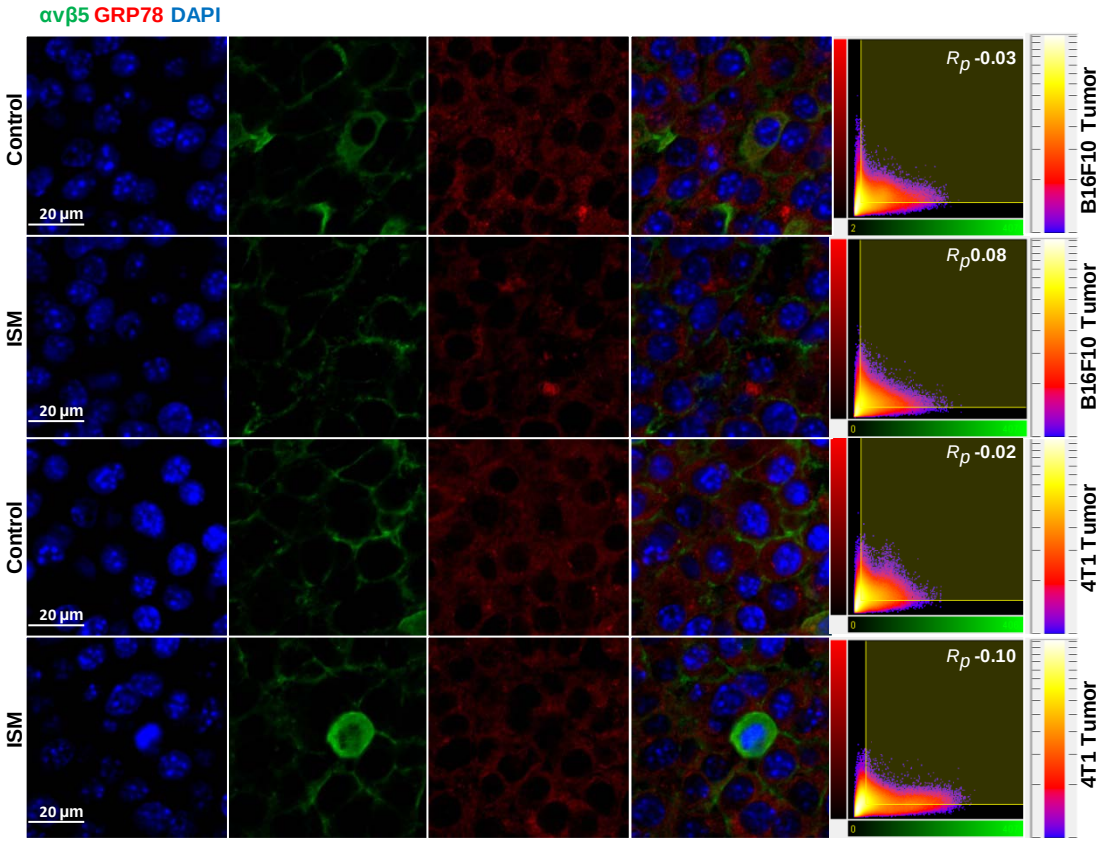
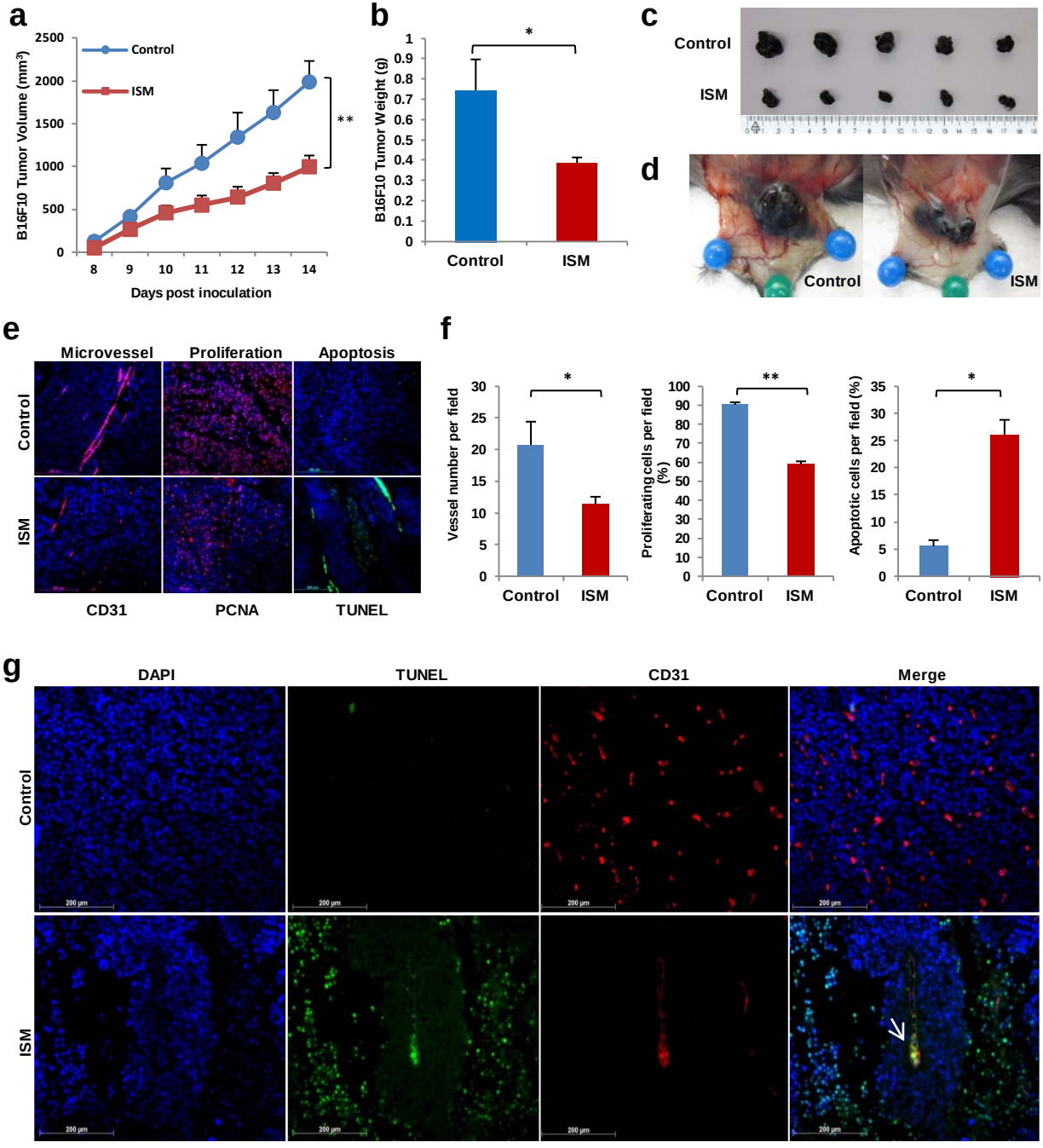

αvβ5 GRP78 DAPI
Control
ISM
Control
ISM
20 μm
20 μm
20 μm
20 μm
R_p -0.03
R_p 0.08
R_p -0.02
R_p -0.10
B16F10 Tumor
B16F10 Tumor
4T1 Tumor
4T1 Tumor

Fig.S8


a
B16F10 Tumor Volume (mm³)
Control
ISM
**
Days post inoculation
b
B16F10 Tumor Weight (g)
*
Control
ISM
c
Control
ISM
d
Control
ISM
e
Microvessel
Proliferation
Apoptosis
Control
ISM
CD31
PCNA
TUNEL
f
Vessel number per field
Proliferating cells per field (%)
Apoptotic cells per field (%)
Control
ISM
g
DAPI
TUNEL
CD31
Merge
Control
ISM
200 μm