

# Supplementary Material: VDAC1 Silencing in Cancer Cells Leads to Metabolic Reprogramming That Modulates the Tumor Microenvironment

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## Text S1: Methods

Here, we present the complete obtained data that in the form of tables with selected representative results were presented in the main article in the form of figures. Briefly, the study was designed to address the relationship between tumor metabolism and the tumor microenvironment (TME), we used siRNA specifically with human VDAC1, as shown previously and here, that it disrupts cancer energy and metabolism homeostasis and induces metabolic reprogramming in the cancer cells derived from human cells. This allows us to follow how metabolic reprogramming of cancerous affects the properties of non-cancerous cells (TME) within the tumor. To explore the interplay between metabolic reprogramming of cancer cells and non-cancerous cells representing the TME within the tumor, we performed a next-generation sequencing (NGS) analysis of human A549 cell-derived tumors in a mouse model treated with non-targeting si-RNA (si-NT) or with siRNA specifically targeting human VDAC1 (si-hVDAC1-2A). As the NGS analysis allows for distinguishing between genes of human and mouse origin, we were able to demonstrate the tumor–host interactions in lung cancer.

### Determination of Mitochondrial Membrane Potential and of Cellular ATP Levels

Mitochondrial membrane potential ( $\Psi$ ) was determined using tetramethylrhodamine methylester (TMRM) dye. A549 cells were transfected with si-NT or si-hVDAC1 and 48 or 72 h post-transfection, were incubated with TMRM (700 nM, 30 min) and washed with PBS. TMRM fluorescence was measured with an Infinite M1000 plate reader. FCCP served as a control for  $\Psi$  dissipation.

Cellular ATP levels were estimated using a luciferase-based assay (CellTiter-Glo, Promega). A549 cells were transfected with si-NT or si-hVDAC1 and 36 h post-transfection were washed twice with PBS and seeded in 96-well plates at densities of  $5 \times 10^4$  cells/ml. ATP levels were assayed according to the manufacturer's protocol and luminescence was recorded using an Infinite M1000 plate reader (Tecan, Männedorf, Switzerland).

**Table S1.** Antibodies used in this study.

Antibody	Source and Cat. No.	Dilution		
		IHC	WB	IF
Mouse monoclonal anti-ATP synthase 5a	Abcam, Cambridge, UK, ab14748	1:300	1:1000	-
Mouse monoclonal anti-Actin	Millipore, Billerica, MA, MAB1501	-	1:40000	-
Rabbit polyclonal anti-Citrate Synthase	Abcam, Cambridge, UK ab96600	1:200	1:4000	-
Rabbit polyclonal anti-CD31	Abcam, Cambridge, UK ab28364	1:300		-
Rabbit monoclonal anti-GLUT1	Abcam, Cambridge, UK ab40084	1: 200	1: 1500	-
Mouse monoclonal anti-GAPDH	Abcam, Cambridge, UK, ab9484	1: 200	1:1000	-
Rabbit monoclonal anti-HK-I	Abcam, Cambridge, UK, ab150423	-	-	1:200
Rabbit monoclonal anti-LDH	Abcam, Cambridge, UK, ab52488	-	-	1:300

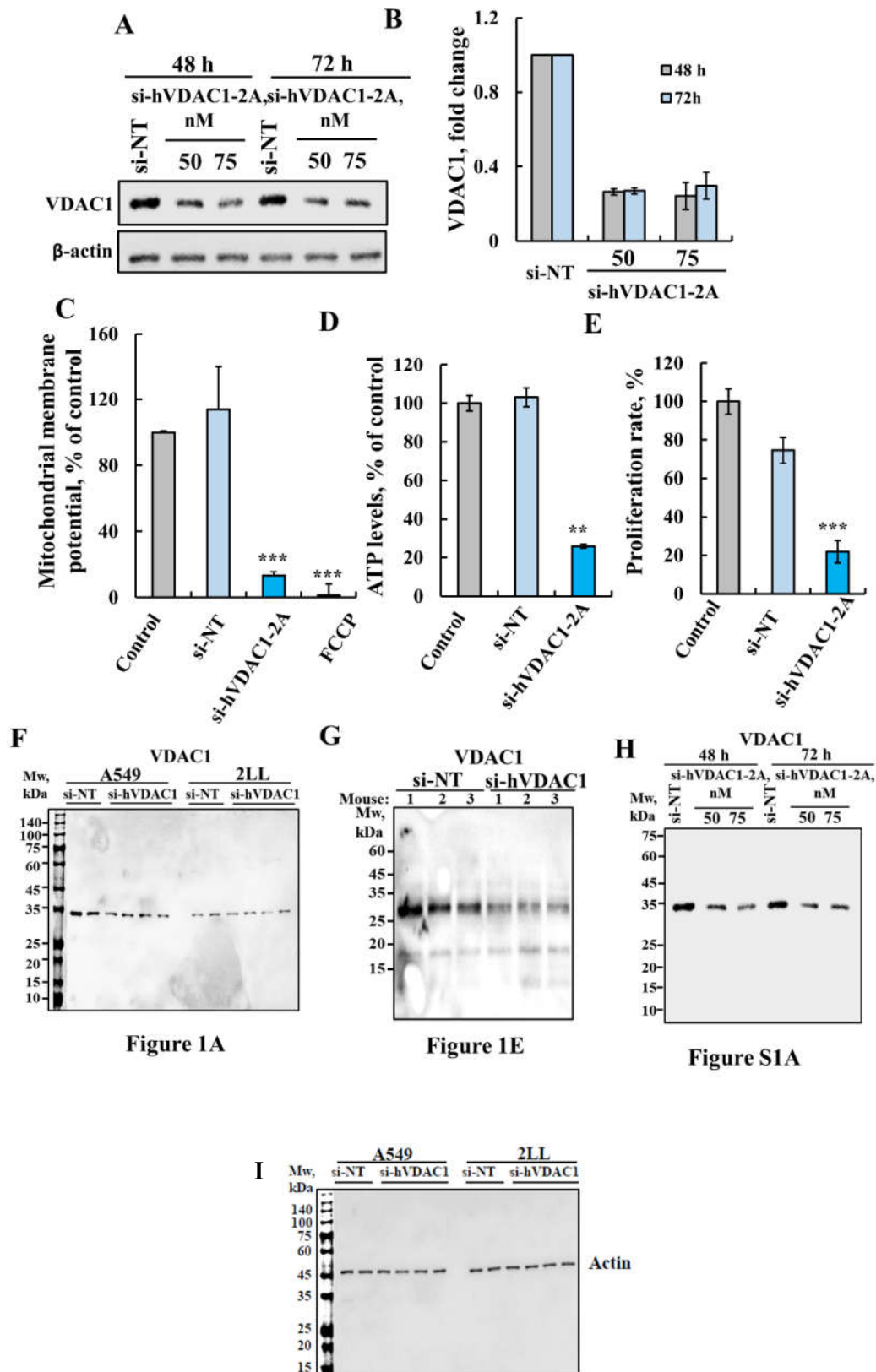
Rabbit monoclonal anti-Tenascin C	Abcam, Cambridge, UK, ab108930	-	-	1:100
Rabbit anti-Periostin	Abcam, Cambridge, UK, ab14041	-	-	1:200
Rabbit monoclonal anti-VDAC1	Abcam, Cambridge, UK, ab154856	1:500	1:5000	1:500
Goat anti-Rabbit (HRP)	KPL, Gaithersburg, USA, 474-1506	1:250	1:15,000	-
Goat anti-Mouse (HRP)	Abcam, Cambridge, UK, ab97040	1:250	1:10,000	-
Donkey anti-Mouse (Alexa Fluor 488)	Abcam, Cambridge, UK, ab150109	-	-	1:500
Goat anti-Rabbit IgG H&L (Alexa Fluor 555)	Abcam, Cambridge, UK, ab150086	-	-	1:500
Donkey anti-Mouse (Alexa Fluor 555)	Abcam, Cambridge, UK, ab150110	-	-	1:500
Goat anti-Rabbit IgG H&L (Alexa Fluor 488)	Life technology, A-11008	-	-	1:500

Antibodies against the indicated protein, their catalogue number, source and the dilutions used in immunohistochemistry (IHC), immunofluorescence (IF) and immunoblot are presented.

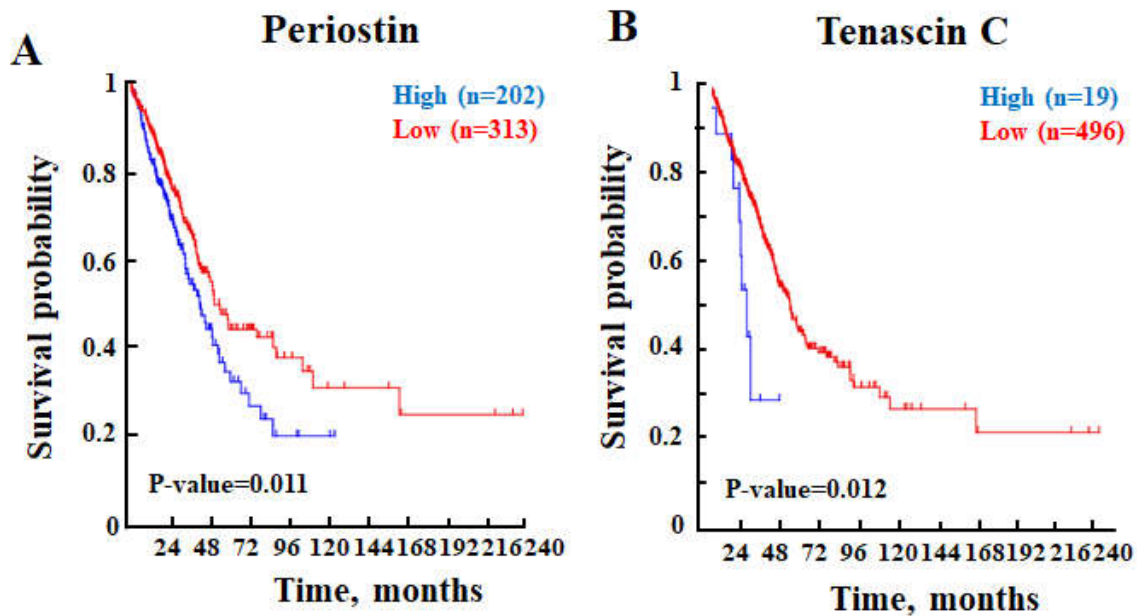
**Table S2.** Real-time PCR primers used in this study.

Gene	Primer Sequences
<i>COL4A1</i>	Forward 5'- GGCCCTTCATTAGCAGGTGT -3' Reverse 5'- GTGAGGACCAACCGTTAGGG -3'
<i>COL5A1</i>	Forward 5'- GATGGCGAATACTGGGTCGAT -3' Reverse 5'- CCAAGAAGTGATTCTGGCTCCCT -3'
<i>LOX</i>	Forward 5'- CCCAGCCACATAGATCGCAT -3' Reverse 5'- CGGGAGACCGTACTGGAAGT -3'
<i>MMP2</i>	Forward 5'- AACGGTCGGGAATACAGCAG -3' Reverse 5'- GTAAACAAGGCTTCATGGGGG -3'
<i>POSTN</i>	Forward 5'- CCCGCAGTGATGCCTATTGA -3' Reverse 5'- CTCCCAAGCCTCGTTACTCG -3'
<i>PLOD2</i>	Forward 5'- AGAGATATGACCTTACAAAGGGAAA -3' Reverse 5'- GCAGTTGATATCAGCCGTCCA -3'
<i>TGFB2</i>	Forward 5'- AAAATCGACATGCCGTCCCA -3' Reverse 5'- ATGGCATCAAGGTACCCACAG -3'

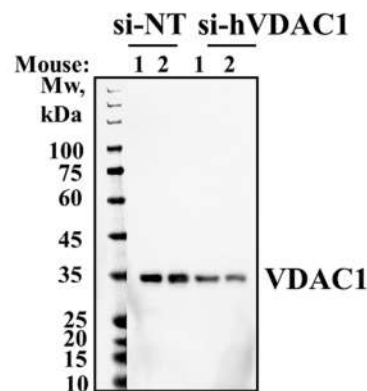
Names of the genes examined and forward and reverse sequences of the primers used are indicated.



(trifluoromethoxy)phenylhydrazine), (25  $\mu$ M) served as control for decreasing  $\Delta\Psi$  levels. The results are the mean \*\*  $P \leq .01$ ; \*\*\*  $P \leq 0.001$ . Uncropped Western Blot of Fig. 1A (F), Fig. 1E (G) and Fig. S1A (H),  $\beta$ -actin bands (I).



**Figure S2.** Decreased survival of patients with adenocarcinoma with high expression levels of periostin or tenascin C. (A,B) Kaplan–Meier analysis of overall survival curves of patients with adenocarcinoma based on low or high expression of periostin (A) or tenascin C (B). The  $p$ -values are indicated.



**Figure S3.** Uncropped Western Blot of Figure 9C.

**Table S3.** VDAC1 silencing in a A549 lung cancer-derived tumor alters the expression of mouse\_ECM-related structural genes.

No	Gene Name (Ensembl)	Fold change- si-hVDAC1/siNT ( $P$ value)	Proposed Function
<b>Collagen and collagen associated proteins</b>			
1	<i>Collagen, type XXVII, alpha 1 (Col27a1)</i> (ENSMUSG00000045672)	−1.93 (0.0766)	Plays a role during cartilage calcification and in the transition of cartilage to bone

2	Collagen, type XVIII, alpha 1 (Col18a1) (ENSMUSG00000001435)	−1.99 (0.0031)	Regulates ECM-dependent motility and morphogenesis of endothelial and non-endothelial cells. Inhibits endothelial cell proliferation and angiogenesis by binding to heparan sulfate proteoglycans
3	Wingless-type MMTV integration site family, member 5A (Wnt5a) (ENSMUSG000000021994)	−2 (0.0159)	Inhibits type II collagen expression in chondrocytes
4	Cartilage associated protein (Crtap) (ENSMUSG000000032431)	−2.18 (0.001)	Required for efficient 3-hydroxylation of fibrillar collagen prolyl residues
5	Collagen, type XVI, alpha 1 (Col16a1) (ENSMUSG000000040690)	−2.37 (5.66E−05)	Involved in mediating cell attachment and induces integrin-mediated cellular reactions, such as cell spreading and alterations in cell morphology
6	Collagen, type IV, alpha 2 (Col4a2) (ENSMUSG000000031503)	−2.57 (0.0223)	Major structural component of glomerular basement membranes, forming a 'chicken-wire' meshwork together with laminins, proteoglycans and entactin/nidogen
7	Procollagen C-endopeptidase enhancer protein (Pcolce) (ENSMUSG000000029718)	−2.58 (0.0279)	Binds to the C-terminal propeptide of type I procollagen and enhances its C-proteinase activity
8	Collagen, type XIII, alpha 1 (Col13a1) (ENSMUSG000000058806)	−2.58 (0.0322)	Involved in cell-matrix and cell-cell adhesion interactions required for normal development
9	Collagen, type V, alpha 2 (Col5a2) (ENSMUSG000000026042)	−2.75 (0.0215)	Group I collagen (fibrillar-forming collagen)
10	Collagen, type IV, alpha 1 (Col4a1) (ENSMUSG000000031502)	−2.76 (0.016)	Major structural component of glomerular basement membranes, forming a 'chicken-wire' meshwork together with laminins, proteoglycans and entactin/nidogen
11	Collagen, type VI, alpha 1 (Col6a1) (ENSMUSG000000001119)	−2.81 (0.0088)	Cell-binding protein
12	Bone morphogenetic protein 1 (Bmp1) (ENSMUSG0000000022098)	−2.85 (0.0009)	Cleaves the C-terminal propeptides of procollagen I, II and III
13	Collagen, type VI, alpha 2 (Col6a2) (ENSMUSG000000020241)	−2.91 (0.0054)	Cell-binding protein
14	Collagen, type V, alpha 3 (Col5a3) (ENSMUSG000000004098)	−2.96 (0.0035)	Cell-matrix adhesion protein binds to DNA, heparan sulfate, thrombospondin, heparin, and insulin
15	Collagen, type XXIV, alpha 1 (Col24a1) (ENSMUSG000000028197)	−3.01 (0.0114)	ECM structural component
16	Biglycan (Bgn) (ENSMUSG000000031375)	−3.03 (0.0081)	May be involved in collagen fiber assembly
17	Collagen, type I, alpha 1 (Col1a1) (ENSMUSG000000001506)	−3.15 (0.0149)	Group I collagen (fibrillar-forming collagen)
18	Collagen, type V, alpha 1 (Col5a1) (ENSMUSG000000026837)	−3.2 (0.0076)	Group I collagen (fibrillar-forming collagen).
19	Collagen, type XXIII, alpha 1 (Col23a1) (ENSMUSG0000000063564)	−3.29 (0.0013)	Collagen biosynthesis and modifying enzymes. Collagen degradation
20	Collagen, type I, alpha 2 (Col1a2) (ENSMUSG000000029661)	−3.3 (0.012)	Group I collagen (fibrillar-forming collagen).
21	Collagen, type VI, alpha 3 (Col6a3) (ENSMUSG000000048126)	−3.34 (0.003)	Cell-binding protein. ECM organization
22	Collagen, type VIII, alpha 1 (Col8a1) (ENSMUSG0000000068196)	−3.44 (0.0248)	Necessary for migration and proliferation of vascular smooth muscle cells and thus for maintaining vessel wall integrity and structure in atherogenesis
23	Collagen, type III, alpha 1 (Col3a1) (ENSMUSG000000026043)	−3.49 (0.0045)	Occurs in most soft connective tissues along with type I collagen
24	Collagen, type XII, alpha 1 (Col12a1) (ENSMUSG000000032332)	−3.7 (0.0096)	Interacts with type I collagen-containing fibrils
25	Collagen triple helix repeat-containing 1 (Cthrc1) (ENSMUSG000000054196)	−3.75 (0.013)	Act as a negative regulator of collagen matrix deposition
26	Collagen, type XIV, alpha 1 (Col14a1) (ENSMUSG000000022371)	−3.98 (0.0003)	Plays an adhesive role by integrating collagen bundles, and may associated with the surface of interstitial collagen fibrils via COL1
27	Collagen, type VIII, alpha 2 (Col8a2) (ENSMUSG000000056174)	−4.17 (0.0156)	Necessary for migration and proliferation of vascular smooth muscle cells
28	Fibromodulin (Fmod) (ENSMUSG000000041559)	−4.32 (0.03)	Affects the rate of fibrils formation. May play a primary role in collagen fibrillogenesis
29	Collagen, type XI, alpha 1 (Col11a1) (ENSMUSG000000027966)	−4.39 (0.018)	May play an important role in fibrillogenesis by controlling lateral growth of collagen II fibrils
30	Podocan (Podn) (ENSMUSG000000028600)	−6.55 (2.04E−09)	Binds to type I collagen. Negatively regulates cell proliferation and migration in smooth muscle cells

Laminin and laminin-associated proteins		
31	Laminin, beta 2 ( <i>Lamb2</i> ) (ENSMUSG00000052911)	−1.86 (0.0021) Binds to cells via a high affinity receptor
32	Laminin, gamma 1 ( <i>Lamc1</i> ) (ENSMUSG00000026478)	−2.06 (0.0081) Binds to cells via a high affinity receptor
	Anthrax toxin receptor 2 ( <i>ANTXR2</i> ) (ENSMUSG00000029338)	−2.17 (0.002) Required for cellular interactions with laminin and the ECM
33	Laminin, alpha 2 ( <i>Lama2</i> ) (ENSMUSG00000019899)	−2.34 (0.0938) Binds to cells via a high affinity receptor
34	Laminin B1 ( <i>Lamb1</i> ) (ENSMUSG00000002900)	−2.45 (0.00046) Binds to cells via a high affinity receptor
	Thrombospondin 1 ( <i>Thbs1</i> ) (ENSMUSG00000040152)	−2.53 (0.0054) Adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions. Can bind to fibrinogen, fibronectin, laminin, type V collagen and integrins alpha-V/beta-1, alpha-V/beta-3 and alpha-IIb/beta-3
35	Laminin, alpha 4 ( <i>Lama4</i> ) (ENSMUSG00000019846)	−2.72 (0.0139) Binds to cells via a high affinity receptor
	Slit homolog 2 ( <i>Drosophila</i> ) ( <i>Slit2</i> ) (ENSMUSG00000031558)	−4.05 (0.016691) Laminin-1 binding
36	Lumican ( <i>Lum</i> ) (ENSMUSG00000036446)	−4.2 (6.33E−08) Laminin binding
Fibronectin		
38	Periostin, osteoblast specific factor ( <i>Postn</i> ) (ENSMUSG00000027750)	−2.51 (0.0105) Induces cell attachment and spreading and plays a role in cell adhesion. Enhances incorporation of BMP1 in the fibronectin matrix of connective tissues, and subsequent proteolytic activation of lysyl oxidase
39	Fibronectin 1 ( <i>Fn1</i> ) (ENSMUSG00000026193)	−2.83 (0.0283) Involved in cell adhesion, cell motility, opsonization, wound healing, and maintenance of cell shape and cell shape healing
40	Fibulin 2 ( <i>Fbln2</i> ) (ENSMUSG00000064080)	−3.01 (0.002) Its binding to fibronectin and other ligands is calcium-dependent. May act as an adapter that mediates the interaction between FBN1 and ELN
41	Epidermal growth factor-containing fibulin-like extracellular matrix protein 2 ( <i>Efemp2</i> ) (ENSMUSG00000024909)	−3.22 (0.0016) Belongs to the fibulin family involved in elastic fiber assembly
42	Fibulin 1 ( <i>Fbln1</i> ) (ENSMUSG00000006369)	−4.56 (4.28E−07) Incorporated into fibronectin-containing matrix fibers. May play a role in cell adhesion and migration along protein fibers within the ECM
Nidogen		
43	Nidogen 1 ( <i>Nid1</i> ) (ENSMUSG00000005397)	−2.29 (0.049) Sulfated glycoprotein widely distributed in basement membranes and tightly associated with laminin. Binds to collagen IV and perlecan. May function in cell-ECM interactions
44	Nidogen 2 ( <i>Nid2</i> ) (ENSMUSG00000021806)	−3.4 (0.0138) Cell adhesion glycoprotein. Probably plays a role in cell-extracellular matrix interactions
Fibrillin		
45	Fibrillin 1 ( <i>Fbn1</i> ) (ENSMUSG00000027204)	−2.99 (0.016) Structural component of the 10–12 nm diameter microfibrils of the ECM. Conveys both structural and regulatory properties to load-bearing connective tissues
46	Fibrillin 2 ( <i>Fbn2</i> ) (ENSMUSG00000024598)	−3.07 (0.057) Fibrillin-2-containing microfibrils regulate the early process of elastic fiber assembly
Collagen synthesis-associated proteins		
47	Arginase-1 ( <i>ARG1</i> ) (ENSMUSG00000019987)	4.55 (0.0098) Key element of the urea cycle, converting L-arginine to urea and L-ornithine, which is further metabolized into the metabolites proline and polyamides that drive collagen synthesis
48	Translocating chain-associated membrane protein 2 ( <i>TRAM2</i> ) (ENSMUSG00000041779)	−1.8 (0.057) Necessary for collagen type I synthesis
Heparan sulfate-associated genes		
49	Heparan sulfate glucosamine 3-O-sulfotransferase 6 ( <i>HS3ST6</i> ) (ENSMUSG00000039628)	14.15 (0.058) Utilizes 3'-phospho-5'-adenylyl sulfate to catalyze the transfer of a sulfo group to heparan sulfate
50	Bifunctional heparan sulfate N-deacetylase/N-sulfotransferase 1 ( <i>NDST1</i> ) (ENSMUSG000000054008)	−1.68 (0.003) Participates in biosynthesis of heparan sulfate serving as L-selectin ligands, thereby playing a role in inflammatory response
51	Xylosyltransferase 2 ( <i>XYLT2</i> ) (ENSMUSG00000020868)	−1.7 (0.032) Involved in formation of heparan sulfate and chondroitin sulfate proteoglycans
52	Exostosin-2 ( <i>EXT2</i> ) (ENSMUSG00000027198)	−1.7 (0.0008) Glycosyltransferase required for biosynthesis of heparan sulfate

53	<i>Exostoses (Multiple)-like 3 (EXTL3)</i> (ENSMUSG00000021978)	−1.72 (0.0001)	Glycosyltransferase which regulates biosynthesis of heparan sulfate
54	<i>Glypican 1 (Gpc1)</i> (ENSMUSG00000034220)	−1.76 (0.0003)	Cell surface proteoglycan that bears heparan sulfate
55	<i>Glypican 4 (Gpc4)</i> (ENSMUSG00000031119)	−1.86 (0.0163)	Cell surface proteoglycan that bears heparan sulfate
56	<i>Heparan sulfate 2-O-sulfotransferase 1 (HS2ST1)</i> (ENSMUSG00000040151)	−1.98 (0.00001)	Catalyzes transfer of sulfate to the C2-position of selected hexuronic acid residues within maturing heparan sulfate
57	<i>Perlecan (heparan sulfate proteoglycan 2) (Hspg2)</i> (ENSMUSG00000028763)	−2.18 (0.007)	Integral component of basement membranes where it is responsible for the fixed negative electrostatic charge and is involved in charge-selective ultrafiltration
58	<i>Heparan sulfate glucosamine 3-O-sulfotransferase 1 (HS3ST1)</i> (ENSMUSG00000051022)	−2.27 (0.03)	Catalyzes the rate-limiting step in heparan sulfate biosynthesis
59	<i>Glypican 6 (Gpc6)</i> (ENSMUSG00000058571)	−2.38 (0.0471)	Cell surface proteoglycan that bears heparan sulfate. Putative cell surface co-receptor for growth factors, extracellular matrix proteins, proteases and anti-proteases
60	<i>Glypican 3 (Gpc3)</i> (ENSMUSG00000055653)	−2.68 (0.05482)	Cell surface proteoglycan that bears heparan sulfate
61	<i>Extracellular sulfatase Sulf-1 (SULF1)</i> (ENSMUSG00000016918)	−2.72 (0.03)	Diminishes heparan sulfate proteoglycan sulfation. Inhibits signaling by heparin-dependent growth factors. Diminishes proliferation
62	<i>Heparan sulfate glucosamine 3-O-sulfotransferase 6 (HS3ST6)</i> (ENSMUSG00000039628)	14.15 (0.058)	Utilizes 3'-phospho-5'-adenylyl sulfate to catalyze the transfer of a sulfo group to heparan sulfate
63	<i>Bifunctional heparan sulfate N-deacetylase/N-sulfotransferase 1 (NDST1)</i> (ENSMUSG00000054008)	−1.68 (0.003)	Participates in biosynthesis of heparan sulfate serving as L-selectin ligands, thereby playing a role in inflammatory response
64	<i>Xylosyltransferase 2 (XYLT2)</i> (ENSMUSG000000020868)	−1.7 (0.032)	Involved in formation of heparan sulfate and chondroitin sulfate proteoglycans
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66	<i>Exostoses (Multiple)-like 3 (EXTL3)</i> (ENSMUSG00000021978)	−1.72 (0.0001)	Glycosyltransferase which regulates biosynthesis of heparan sulfate
67	<i>Glypican 1 (Gpc1)</i> (ENSMUSG00000034220)	−1.76 (0.0003)	Cell surface proteoglycan that bears heparan sulfate
68	<i>Glypican 4 (Gpc4)</i> (ENSMUSG00000031119)	−1.86 (0.0163)	Cell surface proteoglycan that bears heparan sulfate
69	<i>Heparan sulfate 2-O-sulfotransferase 1 (HS2ST1)</i> (ENSMUSG00000040151)	−1.98 (0.00001)	Catalyzes transfer of sulfate to the C2-position of selected hexuronic acid residues within maturing heparan sulfate
70	<i>Perlecan (heparan sulfate proteoglycan 2) (Hspg2)</i> (ENSMUSG00000028763)	−2.18 (0.007)	Integral component of basement membranes where it is responsible for the fixed negative electrostatic charge and is involved in charge-selective ultrafiltration
71	<i>Heparan sulfate glucosamine 3-O-sulfotransferase 1 (HS3ST1)</i> (ENSMUSG00000051022)	−2.27 (0.03)	Catalyzes the rate-limiting step in heparan sulfate biosynthesis
72	<i>Glypican 6 (Gpc6)</i> (ENSMUSG00000058571)	−2.38 (0.0471)	Cell surface proteoglycan that bears heparan sulfate. Putative cell surface co-receptor for growth factors, extracellular matrix proteins, proteases and anti-proteases
73	<i>Glypican 3 (Gpc3)</i> (ENSMUSG00000055653)	−2.68 (0.05482)	Cell surface proteoglycan that bears heparan sulfate

Selected mouse genes from the down-regulated and up-regulated groups associated with ECM structure. The proposed function indicated. For each gene, the gene symbol and name, fold change in expression and *p*-value are indicated. Negative numbers reflect down-regulation.

**Table S4.** VDAC1 silencing in A549 lung cancer-derived tumor alters the expression of mouse ECM-organizing genes.

No	Gene Name (Ensembl)	Fold change- si- hVDAC1/si-NT ( <i>P</i> value)	Proposed Function
ECM Organization			
1	<i>Procollagen-lysine,2-oxoglutarate 5-dioxygenase 3 (PLOD3)</i> (ENSMUSG00000004846)	−1.6 (0.046)	Forms hydroxylysine residues in Xaa-Lys-Gly sequences in collagens that serve as sites of attachment for carbohydrate units and which are essential for the stability of intermolecular collagen cross-links
2	<i>Decorin (Dcn)</i> (ENSMUSG00000019929)	−1.9 (0.031697)	ECM organization.

3	Cysteine-rich secretory protein LCCL domain-containing 2 (Crispld2) (ENSMUSG00000031825)	−2.03 (0.0241)	Promotes matrix assembly
4	von Willebrand factor A domain-containing 1 (Vwa1) (ENSMUSG00000042116)	−2.03 (0.037102)	Promotes matrix assembly
5	Alpha-1-syntrophin (SNTA1) (ENSMUSG00000027488)	−2.12 (0.0007)	Adapter protein that binds to and probably organizes the sub-cellular localization of a variety of membrane proteins. May link various receptors to the actin cytoskeleton and the ECM via the dystrophin glycoprotein complex
6	Tenascin C (Tnc) (ENSMUSG00000028364)	−2.41 (0.0221)	Extracellular matrix protein
7	Layilin (LAYN) (ENSMUSG00000060594)	−2.44 (0.058)	Receptor for hyaluronate
8	Olfactomedin-like 2B (Olfml2b) (ENSMUSG00000038463)	−2.53 (0.0368)	Extracellular matrix binding
9	Prolyl 3-hydroxylase 1 (P3h1) (ENSMUSG00000028641)	−2.71 (0.005153)	Catalyzes the post-translational formation of 3-hydroxyproline in Xaa-Pro-Gly sequences in collagens, especially types IV and V
10	Matrix-remodeling-associated protein 7 (MXRA7) (ENSMUSG00000020814)	−2.76 (0.009)	ECM protein
11	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 (PLOD2) (ENSMUSG00000032374)	−2.8 (0.016)	Forms hydroxylysine residues in Xaa-Lys-Gly sequences in collagens essential for the stability of intermolecular collagen cross-links
12	Discoidin domain-containing receptor 2 (DDR2) (ENSMUSG00000026674)	−2.8 (0.0002)	Tyrosine kinase that functions as cell surface receptor for fibrillar collagen and regulates remodeling of the ECM by up-regulating the collagenases MMP1, MMP2 and MMP13
13	Peroxidasin (Pxdn) (ENSMUSG00000020674)	−3.04 (0.000009)	Plays a role in ECM formation
14	Serine (or cysteine) peptidase inhibitor, clade E, member 2 (Serpine2) (ENSMUSG00000026249)	−3.08 (0.0168)	Serine protease inhibitor. Promotes neurite extension by inhibiting thrombin. Binds heparin
15	Versican (Vcan) (ENSMUSG00000021614)	−3.31 (0.0008)	May play a role in intercellular signaling and in connecting cells with the ECM
16	Proline arginine-rich end leucine-rich repeat (Prep) (ENSMUSG00000041577)	−3.36 (0.0002)	May anchor basement membranes to underlying connective tissue
17	Olfactomedin-like 2A (Olfml2a) (ENSMUSG00000046618)	−3.56 (0.0016)	ECM organization
18	SPARC-related modular calcium-binding 1 (Smoc1) (ENSMUSG00000021136)	−3.82 (0.006)	ECM organization
19	Fras1-related extracellular matrix protein 1 (Frem1) (ENSMUSG00000059049)	−3.83 (0.0324)	Plays a role in epidermal differentiation and required for epidermal adhesion during embryonic development
20	Tolloid-like protein 1 (TLL1) (ENSMUSG00000053626)	−3.88 (0.002)	Protease processing of procollagen Cpropeptides, such as chordin, pro-biglycan and pro-lysyl oxidase. ECM disassembly
21	ABI gene family, member 3 (NESH)-binding protein (Abi3bp) (ENSMUSG00000035258)	−4.18 (0.0000000003)	ECM organization
22	Homeobox protein Mohawk (MKX) (ENSMUSG00000061013)	−5.16 (0.027)	Collagen fibril organization and morphogenetic regulator of cell adhesion
<b>Other ECM organization-associated genes</b>			
23	F-box/LRR-repeat protein 14 (FBXL14) (ENSMUSG00000030019)	1.53 (0.047)	Stimulates SNAIL1 degradation
24	Zinc finger E-box-binding homeobox 1 (ZEB1) (ENSMUSG00000024238)	−1.91 (0.056)	Acts as a transcriptional regulator in mesenchymal cells. Represses E-cadherin promoter. Induces epithelial-mesenchymal transition
25	Kielin/chordin-like protein (KCP) (ENSMUSG00000059022)	−2.07 (0.06)	Enhances bone morphogenetic protein signaling in a paracrine manner. Inhibits both the activin-A and TGFβ1-mediated signaling pathways
26	Protein TMEPAI (PMEPA1) (ENSMUSG00000038400)	−2.1 (0.006)	Functions as a negative regulator of TGF-beta signaling
27	Neogenin (NEO1) (ENSMUSG00000032340)	−2.52 (0.0017)	Negative regulator of BMP signaling pathway
28	Vasorin (VASN) (ENSMUSG00000039646)	−2.55 (0.004)	Inhibitor of TGF-beta signaling.
29	Zinc finger protein SNAIL1 (SNAIL1) (ENSMUSG00000042821)	−3.07 (0.01)	Transcriptional regulator in mesenchymal cells. Represses E-cadherin promoter. Induces epithelial-mesenchymal transition



30	<i>Twist-related protein 1 (TWIST1)</i> (ENSMUSG000000035799)	−3.19 (0.001)	Transcriptional regulator in mesenchymal cells. Represses E-cadherin promoter. Induces an epithelial-mesenchymal transition. Homodimers induce expression of FGFR2 and POSTN while heterodimers repress FGFR2 and POSTN expression and induce THBS1 expression
31	<i>Prolyl 4-hydroxylase subunit alpha-3</i> (P4HA3) (ENSMUSG000000051048)	−3.68 (0.005)	Catalyzes the post-translational formation of 4-hydroxyproline in Xaa-Pro-Gly sequences in collagens and other proteins
32	<i>Bone morphogenetic protein receptor type-1B (BMPR1B)</i> (ENSMUSG000000052430)	−4.12 (0.015)	BMP signaling pathway

Selected mouse genes from the down-regulated and up-regulated groups associated with ECM organization with their proposed function indicated. For each gene, the gene symbol and name, fold change in expression and p-value are indicated. Negative numbers reflect down-regulation.

**Table S5.** VDAC1 silencing in A549 lung cancer-derived tumour alters the expression of mouse ECM-remodelling-associated genes.

No	Gene Name (Ensembl)	Fold change-sihVDAC1/si-NT (P value)	Proposed Function
<b>Metalloproteinases</b>			
1	<i>Macrophage metalloelastase (MMP12)</i> (ENSMUSG000000049723)	4.4 (0.010)	May be involved in tissue injury and remodeling. Has significant elastolytic activity
2	<i>Tissue inhibitor of metalloproteinase 1 (Timp1)</i> (ENSMUSG000000001131)	−2.11 (0.1063)	Metalloproteinase inhibitor
3	<i>matrix metalloproteinase 17 (Mmp17)</i> (ENSMUSG000000029436)	−2.3 (0.1049)	Endopeptidase that degrades various components of the ECM, such as fibrin. Involved in the activation of membrane-bound precursors of growth factors or inflammatory mediators
4	<i>Tissue inhibitor of metalloproteinase 2 (Timp2)</i> (ENSMUSG000000017466)	−2.38 (0.0049)	Complexes with metalloproteinases (such as collagenases) and irreversibly inactivates them.
5	<i>Reversion-inducing cysteine-rich protein with Kazal motifs (RECK) (ENSMUSG000000028476)</i>	−2.51 (0.008)	Negatively regulates MMP-9. Appears to also regulate MMP-2 and MT1-MMP, which are involved in cancer progression
6	<i>Matrix metalloproteinase 14 (membrane-inserted) (Mmp14) (ENSMUSG00000000957)</i>	−2.55 (0.0117)	Endopeptidase that degrades various components of the extracellular matrix, such as collagen. Activates progelatinase A. Essential for pericellular collagenolysis
7	<i>Matrix metalloproteinase 23 (Mmp23)</i> (ENSMUSG000000029061)	−2.57 (0.0566)	Metalloproteinase. Regulates the surface expression of some potassium channels by retaining them in the ER
8	<i>Matrix metalloproteinase 11 (Mmp11)</i> (ENSMUSG00000000901)	−2.8 (0.0009)	Extracellular matrix disassembly, collagen catabolic process. May play an important role in the progression of epithelial malignancies
9	<i>Discoidin domain-containing receptor 2 (DDR2)</i> (ENSMUSG000000026674)	−2.8 (0.0002)	Tyrosine kinase that functions as cell surface receptor for fibrillar collagen and regulates remodeling of the extracellular matrix, by up-regulation of the collagenases MMP1, MMP2 and MMP13
10	<i>Matrix metalloproteinase 13 (Mmp13)</i> (ENSMUSG000000050578)	−3.17 (0.0178)	Plays a role in the degradation of extracellular matrix proteins including fibrillar collagen, fibronectin, TNC and ACAN
11	<i>Matrix metalloproteinase 3 (Mmp3)</i> (ENSMUSG000000043613)	−3.46 (0.0078)	Can degrade fibronectin, laminin, gelatins of type I, III, IV, and V; collagens III, IV, X, and IX, and cartilage proteoglycans
12	<i>Matrix metalloproteinase 27 (Mmp27)</i> (ENSMUSG000000070323)	−3.48 (0.1157)	Metalloendopeptidase activity degrade protein components of the extracellular matrix such as fibronectin, laminin, gelatins and/or collagens
13	<i>Matrix metalloproteinase 9 (Mmp9)</i> (ENSMUSG000000017737)	−4.25 (0.0531)	Cleaves type IV and type V collagen into large C-terminal three quarter fragments and shorter N-terminal one quarter fragments
14	<i>Matrix metalloproteinase 2 (Mmp2)</i> (ENSMUSG000000031740)	−4.27 (3.50E−05)	Cleavage of gelatin type I and collagen types IV, V, VII, X. Cleaves the collagen-like sequence Pro-Gln-Gly-I-Ile-Ala-Gly-Gln
<b>ADAM and ADAMTS</b>			
15	<i>A disintegrin and metalloproteinase domain-containing protein 9 (ADAM9) (ENSMUSG000000031555)</i>	−1.69 (0.031)	Cleaves and releases molecules involved in tumorigenesis and angiogenesis, such as TEK, KDR, EPHB4, CD40, VCAM1 and CDH5. May mediate cell-cell, cell-matrix interactions and regulate the motility of cells via interactions with integrins

16	<i>A disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 9 (Adamts9) (ENSMUSG00000030022)</i>	−1.85 (0.0535)	Extracellular matrix organization, Cleaves the large aggregating proteoglycans, aggrecan and versican
17	<i>A disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 1 (Adamts1) (ENSMUSG00000022893)</i>	−1.9 (0.038)	Cleaves aggrecan, a cartilage proteoglycan, Has angiogenic inhibitor activity. Active metalloprotease, which may be associated with various inflammatory processes as well as development of cancer cachexia
18	<i>GDP-fucose protein O-fucosyltransferase 2 (POFUT2) (ENSMUSG00000020260)</i>	−1.96 (0.006)	Required for the proper secretion of ADAMTS family members such as ADAMSL1 and ADAMST13. O-fucosylation of TSRs, also required for restricting EMT
19	<i>Disintegrin and metalloproteinase domain-containing protein 23 (ADAM23) (ENSMUSG00000025964)</i>	−2.25 (0.065)	May play a role in cell-cell and cell-matrix interactions. Non-catalytic metalloprotease-like protein
20	<i>A disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 5 (aggrecanase-2) (Adamts5) (ENSMUSG00000022894)</i>	−2.45 (0.0184)	ECM-degrading enzyme that shows proteolytic activity toward the hyaluronan group of chondroitin sulfate proteoglycans, including aggrecan, versican, brevican and neurocan.
21	<i>A disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 7 (Adamts7) (ENSMUSG00000032363)</i>	−2.51 (0.04817)	Metalloprotease that may play a role in the degradation of COMP
22	<i>A disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 4 (Adamts4) (ENSMUSG00000006403)</i>	−2.97 (0.0322)	Cleaves aggrecan, a cartilage proteoglycan
23	<i>A disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 2 (Adamts2) (ENSMUSG00000036545)</i>	−2.97 (0.008)	Cleaves the propeptides of type I and II collagen prior to fibril assembly. Does not act on type III collagen
24	<i>A disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 15 (Adamts15) (ENSMUSG00000033453)</i>	−3.45 (0.0042)	Metalloendopeptidase activity
25	<i>Disintegrin and metalloproteinase domain-containing protein 12 (ADAM12) (ENSMUSG00000054555)</i>	−3.7 (0.006)	Metalloprotease activity and ECM organization
26	<i>Disintegrin and metalloproteinase domain-containing protein 22 (ADAM22) (ENSMUSG00000040537)</i>	−4.67 (0.032)	Probable ligand for integrin in the brain. Non-catalytic metalloprotease-like protein. Involved in regulation of cell adhesion and spreading and in inhibition of cell proliferation. Neuronal receptor for LGI1
27	<i>A disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 12 (Adamts12) (ENSMUSG00000047497)</i>	−5.09 (0.0055)	Metalloprotease that plays a role in the degradation of Cartilage oligomeric matrix protein (COMP) (By similarity). Cleaves also alpha-2 macroglobulin and aggrecan. Has anti-tumorigenic properties
28	<i>A disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 3 (Adamts13) (ENSMUSG00000070469)</i>	−5.58 (0.0247)	Metalloendopeptidase activity
29	<i>A disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 16 (Adamts16) (ENSMUSG00000049538)</i>	−8.38 (0.0052)	Metalloendopeptidase activity, tight interaction with ECM
<b>Other metalloproteinases and regulator proteins</b>			
30	<i>Kallikrein-8 (KLK8) (ENSMUSG00000064023)</i>	6.41 (0.019)	Serine protease capable of degrading a number of proteins, such as casein, fibrinogen, kininogen, fibronectin and collagen type IV
31	<i>Prolyl endopeptidase FAP (FAP) (ENSMUSG00000000392)</i>	−3.5 (0.002)	Cell surface glycoprotein serine protease that participates in ECM degradation and involved in many cellular processes including tissue remodeling
32	<i>Tetraspanin-12 (TSPAN12) (ENSMUSG00000029669)</i>	−3.78 (0.0018)	Regulator of membrane proteinases such as ADAM10 and MMP14/MT1-MMP. Activates ADAM10-dependent cleavage activity of amyloid precursor protein (APP). Activates MMP14/MT1-MMP-dependent cleavage activity
33	<i>Pappalysin-1 (PAPPA) (ENSMUSG00000028370)</i>	−4.32 (0.0001)	Metalloproteinase which specifically cleaves IGFBP-4 and IGFBP-5, resulting in release of bound IGF. Cleavage of IGFBP-4 is dramatically enhanced by the presence of IGF, whereas cleavage of IGFBP-5 is slightly inhibited by the presence of IGF
34	<i>Cathepsin K (CTSK) (ENSMUSG00000028111)</i>	−4.97 (0.002)	Plays an important role in ECM degradation
<b>Lysyl oxidase</b>			

35	<i>Lysyl oxidase-like 2 (Loxl2)</i> (ENSMUSG00000034205)	−2.4 (0.0382)	When secreted in ECM, promotes cross-linking of ECM proteins by mediating oxidative deamination of peptidyl lysine residues in precursors to fibrous collagen and elastin
36	<i>Lysyl oxidase homolog 4 (Loxl4)</i> (ENSMUSG000000025185)	−2.51 (0.074)	May modulate formation of a collagenous ECM
37	<i>Lysyl oxidase (Lox)</i> (ENSMUSG000000024529)	−2.6 (0.0484)	Responsible for the post-translational oxidative deamination of peptidyl lysine residues in precursors to fibrous collagen and elastin
38	<i>Lysyl oxidase-like 1 (Loxl1)</i> (ENSMUSG000000032334)	−3.4 (0.0041)	Active on elastin and collagen

Selected mouse genes from the down-regulated and up-regulated groups associated with ECM remodelling. The proposed function indicated. For each gene, the gene symbol and name, fold change in expression and *p*-value are indicated. Negative numbers reflect down-regulation.

**Table S6.** VDAC1 silencing in a A549 lung cancer-derived tumor alters the expression of mouse genes for intercellular-interacting proteins.

No	Gene Name ( Ensembl)	Fold change si-hVDAC1/si-NT (P value)	Proposed Function
<b>Intercellular interaction</b>			
1	<i>Leucine-rich repeat transmembrane protein FLRT3 (FLRT3)</i> (ENSMUSG000000051379)	9.05 (0.020)	Plays a role in cell-cell adhesion via interaction with ADGRL3. Plays a role in fibroblast growth factor-mediated signaling cascades
2	<i>L1 cell adhesion molecule (L1CAM)</i> (ENSMUSG000000031391)	3.43 (0.039)	Neuronal cell adhesion molecule with a strong implication in cell migration
3	<i>Basal cell adhesion molecule (BCAM)</i> (ENSMUSG000000002980)	3.41 (0.023)	Laminin alpha-5 receptor. May mediate intracellular signaling
4	<i>Tensin 1 (TNS1)</i> (ENSMUSG000000055322)	−1.69 (0.021)	Involved in fibrillar adhesion formation. cell-substrate junction assembly
5	<i>Lectin, galactose binding, soluble 1 (Lgals1)</i> (ENSMUSG000000068220)	−1.71 (0.056681)	Lectin that binds beta-galactoside and a wide array of complex carbohydrates
6	<i>Liprin-beta-1 (PPFIBP1)</i> (ENSMUSG000000016487)	−1.84 (0.0002)	Cell adhesion protein
7	<i>Protocadherin gamma subfamily C, 4 (PCDHGC4)</i> (ENSMUSG000000023036)	−1.88 (0.0007)	Potential calcium-dependent cell-adhesion protein
8	<i>Pseudopodium-enriched atypical kinase 1 (PEAK1)</i> (ENSMUSG000000074305)	−1.92 (0.017)	Tyrosine kinase that may play a role in cell spreading and migration on fibronectin
9	<i>Vinculin (VCL)</i> (ENSMUSG000000021823)	−2.01 (0.007)	Actin filament (F-actin)-binding protein involved in cell-matrix adhesion and cell-cell adhesion
10	<i>SPARC related modular calcium binding 2 (Smoc2)</i> (ENSMUSG000000023886)	−2.36 (0.0116)	Promotes matrix assembly and cell adhesiveness
11	<i>Extracellular matrix protein 2, female organ and adipocyte specific (Ecm2)</i> (ENSMUSG000000043631)	−2.4 (0.0513)	Promotes matrix assembly and cell adhesiveness
12	<i>Spondin 1, (f-spondin) extracellular matrix protein (Spon1)</i> (ENSMUSG000000038156)	−2.62 (0.046)	Cell adhesion protein
13	<i>EGF-like, fibronectin type III and laminin G domains (Egflam)</i> (ENSMUSG000000042961)	−2.63 (0.0599)	Promotes matrix assembly and cell adhesiveness
14	<i>Cadherin-2 (CDH2) (NCAD)</i> (ENSMUSG000000024304)	−2.71 (0.075)	Associated with EMT
15	<i>Microfibrillar associated protein 5 (Mfap5)</i> (ENSMUSG000000030116)	−2.71 (0.0266)	Component of the elastin-associated microfibrils
16	<i>Fibulin 5 (Fbln5)</i> (ENSMUSG000000021186)	−2.72 (0.0014)	Essential for elastic fiber formation. Involved in assembly of continuous elastin polymer. Promotes interaction of microfibrils and ELN
17	<i>Carboxypeptidase X 2 (M14 family) (Cpxm2)</i> (ENSMUSG000000030862)	−2.86 (0.0011)	May be involved in cell-cell interactions
18	<i>Microfibrillar-associated protein 2 (Mfap2)</i> (ENSMUSG000000060572)	−2.88 (0.0016)	Component of the elastin-associated microfibrils

19	SPARC-like 1 (Sparc1) (ENSMUSG00000029309)	−2.92 (0.01481)	Interacts with the ECM to create intermediate states of cell adhesion
20	Secreted acidic cysteine rich glycoprotein (Sparc) (ENSMUSG00000018593)	−3.05 (0.01485)	Appears to regulate cell growth through interactions with the ECM and cytokines. Binds calcium and copper, several types of collagen, albumin, thrombospondin, PDGF and cell membranes
21	CD93 antigen (Cd93) (ENSMUSG00000027435)	−3.07 (0.0082)	Interacts with soluble defense collagens. May play a role in intercellular adhesion
22	Neural cell adhesion molecule 1 (NCAM1) (ENSMUSG00000039542)	−3.09 (0.004)	Cell adhesion
23	Coiled-coil domain containing 80 (Ccdc80) (ENSMUSG00000022665)	−3.21 (0.00016)	Promotes cell adhesion and matrix assembly
24	Thrombospondin 2 (Thbs2) (ENSMUSG00000023885)	−3.24 (0.0078)	Adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions. Ligand for CD36 mediating antiangiogenic properties
25	Cadherin-11 (CDH11) (ENSMUSG00000031673)	−3.33 (0.006)	Adhesion protein
26	Microfibrillar-associated protein 4 (Mfap4) (ENSMUSG00000042436)	−3.42 (0.0027)	Could be involved in calcium-dependent cell adhesion or intercellular interactions
27	Cartilage intermediate layer protein, nucleotide pyrophosphohydrolase (Cilp) (ENSMUSG00000042254)	−3.43 (3.50E−05)	Has the ability to suppress IGF1-induced proliferation and sulfated proteoglycan synthesis. Inhibits ligand-induced IGF1R autophosphorylation
28	Leucine-rich repeat-containing protein 15 (LRRC15) (ENSMUSG00000052316)	−3.43 (0.0014)	Collagen binding, fibronectin binding, laminin binding
29	Leucine-rich repeat and fibronectin type-III domain-containing protein 3 (LRFN3) (ENSMUSG00000036957)	−3.49 (0.012)	Cell adhesion molecule that mediates homophilic cell-cell adhesion in a Ca <sup>2+</sup> -independent manner
30	Reelin (Reln) (ENSMUSG00000042453)	−3.58 (0.0506)	ECM serine protease. Enzymatic activity is important for modulation of cell adhesion
31	Thrombospondin-3 (THBS3) (ENSMUSG00000028047)	−3.61 (0.0012)	Adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions. Can bind to fibrinogen, fibronectin, laminin and type V collagen
32	Scavenger receptor cysteine rich family, 5 domains (Ssc5d) (ENSMUSG00000035279)	−4.94 (1.15E−06)	Binds to ECM proteins
33	Protocadherin 17 (PCDH17) (ENSMUSG00000035566)	−5.85 (0.0095)	Homophilic cell adhesion via plasma membrane adhesion molecules
34	Thrombospondin 4 (Thbs4) (ENSMUSG00000021702)	−6.48 (0.0561)	Adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions. Can bind to fibrinogen, fibronectin, laminin and type V collagen
35	Cartilage oligomeric matrix protein (Comp) (ENSMUSG00000031849)	−6.71 (0.000247)	Interaction with ECM proteins, such as the collagens and fibronectin
36	Cadherin-10 (Cdh10) (ENSMUSG00000022321)	−20.43 (0.002)	Homophilic cell adhesion via plasma membrane adhesion molecules
<b>Integrin and growth factors</b>			
37	Integrin beta-4 (ITGB4) (ENSMUSG00000020758)	3.14 (0.093)	Integrin alpha-6/beta-4 is a receptor for laminin. It plays a critical structural role in the hemidesmosome of epithelial cells.
38	Integrin beta (ITGB2) (ENSMUSG00000000290)	3.1 (0.016)	It is a receptor for ICAM1, ICAM2, ICAM3 and ICAM4
39	Integrin alpha-IIb (ITGA2B) (ENSMUSG00000034664)	2.91 (0.044)	Integrin alpha-IIb/beta-3 is a receptor for fibrinogen, fibrinogen, plasminogen, prothrombin, thrombospondin and vitronectin.
40	Integrin alpha-X (ITGAX) (ENSMUSG00000030789)	2.41 (0.104)	Integrin alpha-X/beta-2 is a receptor for fibrinogen. It recognizes the sequence G-P-R in fibrinogen. It mediates cell-cell interaction during inflammatory responses. It is especially important in monocyte adhesion and chemotaxis.
41	Intercellular adhesion molecule 1 (ICAM1) (ENSMUSG00000037405)	2.27 (0.017)	ICAM proteins are ligands for the leukocyte adhesion protein LFA-1 (integrin alpha-L/beta-2).
42	Golgi apparatus protein 1 (Glg1) (ENSMUSG00000003316)	−1.53 (0.012019)	Binds fibroblast growth factor. Binds E-selectin (cell-adhesion lectin on endothelial cells mediating the binding of neutrophils).
43	Integrin alpha-V (ITGAV) (ENSMUSG00000027087)	−1.6 (0.012)	The alpha-V (ITGAV) integrins are receptors for vitronectin, cytotactin, fibronectin, fibrinogen, laminin, matrix metalloproteinase-2, osteopontin, osteomodulin, prothrombin, thrombospondin and vWF.
44	LIM and senescent cell antigen-like-containing domain protein (LIMS1) (ENSMUSG00000019920)	−1.61 (0.016)	Adapter protein in a cytoplasmic complex linking beta-integrins to the actin cytoskeleton, bridges the complex to cell surface receptor tyrosine kinases and growth factor receptors.

45	Latent transforming growth factor beta binding protein 3 (Ltbp3) (ENSMUSG00000024940)	−1.61 (0.0088)	May be involved in the assembly, secretion and targeting of TGF-beta1 to sites at which it is stored and/or activated. May play critical roles in controlling and directing the activity of TGF-beta1. May have a structural role in the ECM.
46	Integrin beta (ITGB5) (ENSMUSG00000022817)	−1.83 (0.022)	Possible receptor for fibronectin.
47	Insulin-like growth factor I (IGF1) (ENSMUSG00000020053)	−1.91 (0.05)	The insulin-like growth factors, isolated from plasma, are structurally and functionally related to insulin but have a much higher growth-promoting activity. Acts as a ligand for IGF1R. Binds to integrins ITGA6:ITGB3 and ITGA6:ITGB4. Its binding to integrins and subsequent ternary complex formation with integrins and IGF1R are essential for IGF1 signaling.
48	Endoglin (ENG) (ENSMUSG00000026814)	−1.92 (0.017)	Acts as TGF-beta co-receptor and is involved in the TGF-beta/BMP signaling cascade that ultimately leads to the activation of SMAD transcription factors
49	TGF-beta receptor type-2 (TGFB2) (ENSMUSG00000032440)	−2.15 (0.012)	Transmembrane serine/threonine kinase forming with the TGF-beta type I serine/threonine kinase receptor.
50	Latent transforming growth factor beta binding protein 2 (Ltbp2) (ENSMUSG00000002020)	−2.24 (0.0678)	Play an integral structural role in elastic-fiber architectural organization and/or assembly. May be involved in the assembly, secretion and targeting of TGF-beta to sites at which it is stored and/or activated. Play critical roles in controlling and directing the activity of TGF-beta. May have a structural role in the ECM.
51	Latent transforming growth factor beta binding protein 1 (Ltbp1) (ENSMUSG00000001870)	−2.25 (0.0245)	Involved in the assembly, secretion and targeting of TGFβ1 to sites at which it is stored and/or activated. May play critical roles in controlling and directing the activity of TGFβ1. May have a structural role in the ECM.
52	Transforming growth factor beta 1 induced transcript 1 (Tgfb1i1) (ENSMUSG00000030782)	−2.55 (0.0053)	Links various intracellular signaling modules to plasma membrane receptors and regulates the Wnt and TGFβ signaling pathways.
53	Transforming growth factor, beta 3 (Tgfb3) (ENSMUSG00000021253)	−2.65 (0.0244)	Regulates molecules involved in cellular adhesion and ECM formation
54	Transforming growth factor, beta 2 (Tgfb2) (ENSMUSG00000039239)	−3.18 (0.0001)	TGF-beta 2 has suppressive effects on interleukin-2 dependent T-cell growth.
55	Cell adhesion molecule 3 (CADM3) (ENSMUSG00000005338)	−3.19 (0.036)	Involved in the cell-cell adhesion.
56	Asporin (Aspn) (ENSMUSG00000021388)	−3.52 (0.0195)	Plays a role in osteoblast-driven collagen biomineralization activity. Critical regulator of TGF-beta in articular cartilage
57	Sushi, von Willebrand factor type A, EGF and pentraxin domain-containing protein 1 (SVEP1) (ENSMUSG00000028369)	−3.63 (0.0035)	Play a role in the cell adhesion process.
58	Epidermal growth factor-containing fibulin-like extracellular matrix protein 1 (Efemp1) (ENSMUSG00000020467)	−3.98 (0.0212)	Binds EGFR, the EGF receptor, inducing EGFR autophosphorylation and the activation of downstream signaling pathways. May play a role in cell adhesion and migration.
59	EGF-like repeats and discoidin I-like domains 3 (Edil3) (ENSMUSG00000034488)	−4.41 (0.0235)	Promotes adhesion of endothelial cells through interaction with the alpha-v/beta-3 integrin receptor. Inhibits formation of vascular-like structures.
60	Integrin beta-like protein 1 (ITGBL1) (ENSMUSG00000032925)	−4.74 (0.0038)	Cell adhesion
61	Nephroblastoma overexpressed gene (Nov) (ENSMUSG00000037362)	−5.12 (0.00197)	Playing a role in various cellular processes including proliferation, adhesion, migration, differentiation and survival. Acts by binding to integrins or membrane receptors such as NOTCH1.
62	Osteoglycin (Ogn) (ENSMUSG00000021390)	−5.48 (5.89E-06)	Induces bone formation in conjunction with TGF-beta-1 or TGF-beta-2.
63	Neurofascin (NFASC) (ENSMUSG00000026442)	−6.65 (0.00005)	Cell adhesion, ankyrin-binding protein which may be involved in neurite extension
64	Integrin binding sialoprotein (IBSP) (ENSMUSG00000029306)	−8.06 (0.0285)	Appears to form an integral part of the mineralized matrix. Probably important to cell-matrix interaction.
65	Tenascin N (TNN) (ENSMUSG00000026725)	−9.59 (9.61E-06)	Extracellular matrix protein that seems to be a ligand for ITGA8:ITGB1, ITGAV, ITGB1 and ITGA4, ITGB1

Selected mouse genes from the down-regulated and up-regulated groups associated with extracellular intercellular-interaction. The proposed function indicated. For each gene, the gene symbol and name, fold change in expression and p-value are indicated. Negative numbers reflect down-regulation.

**Table S7.** Alterations in the expression of angiogenesis-associated mouse genes in a si-hVDAC1-treated A549-derived xenograft.

No	Gene Name (Ensembl)	Fold change si-hVDAC1/si-NT (P value)	Proposed Function
<b>Angiogenesis</b>			
1	<i>Interleukin-12 subunit alpha (IL12A)</i> (ENSMUSG00000027776)	25.86 (0.036)	Angiostatic cytokine
2	<i>Ectonucleotide pyrophosphatase/phosphodiesterase family member 2 (ENPP2)</i> (ENSMUSG00000022425)	16.23 (0.0003)	Acts as an angiogenic factor by stimulating migration of smooth muscle cells and microtubule formation
3	<i>Interferon gamma (IFNG)</i> (ENSMUSG00000055170)	13.26 (0.0128)	Anti-angiogenic factor
4	<i>Zinc finger protein castor homolog 1 (CASZ1)</i> (ENSMUSG00000028977)	10.85 (0.015)	Transcription factor involved in vascular assembly and morphogenesis through direct transcriptional regulation of EGFL7
5	<i>Prospero homeobox protein 1 (PROX1)</i> (ENSMUSG00000010175)	7.28 (0.0112)	Positive regulation of lymphangiogenesis
6	<i>C-X-C motif chemokine 10 (CXCL10)</i> (ENSMUSG00000034855)	5.06 (0.0148)	Anti-angiogenic factor
7	<i>Receptor-type tyrosine-protein kinase FLT3 (FLT3)</i> (ENSMUSG00000042817)	4.66 (0.0154)	Pro-angiogenic factor
8	<i>Protransforming growth factor alpha (TGFA)</i> (ENSMUSG00000029999)	2.76 (0.0373)	Positive regulator of angiogenesis
9	<i>Integrin alpha-V (ITGAV)</i> (ENSMUSG00000027087)	-1.6 (0.012)	Positive regulator of angiogenesis
10	<i>Plexin domain-containing protein 2 (PLXDC2)</i> (ENSMUSG00000026748)	-1.81 (0.011)	Plays a role in tumor angiogenesis
11	<i>A disintegrin-like and metalloproteinase (reprolysin type) with thrombospondin type 1 motif, 1 (Adams1)</i> (ENSMUSG00000022893)	-1.9 (0.038)	Active metalloprotease which may be associated with various inflammatory processes, as well as development of cancer cachexia. Has angiogenic inhibitor activity
12	<i>Angiopoietin-related protein 2 (ANGPTL2)</i> (ENSMUSG00000004105)	-1.91 (0.02)	Pro-angiogenic factor
13	<i>collagen, type XVIII, alpha 1 (Col18a1)</i> (ENSMUSG00000001435)	-1.99 (0.0031)	Potently inhibits endothelial cell proliferation and angiogenesis
14	<i>cysteine rich protein 61 (Cyr61)</i> (ENSMUSG00000028195)	-2.09 (0.0408)	Promotes cell proliferation, chemotaxis, angiogenesis and cell adhesion
15	<i>Von Willebrand factor (Vwf)</i> (ENSMUSG00000001930)	-2.14 (0.063104)	Pro-angiogenic factor
16	<i>perlecan (heparan sulfate proteoglycan 2) (Hspg2)</i> (ENSMUSG00000028763)	-2.18 (0.007)	Positive and negative regulator of angiogenesis
17	<i>Platelet factor 4 (PF4) (ENSMUSG00000029373)</i>	-2.22 (0.0359)	Negative regulator of angiogenesis
18	<i>Neuropilin-1 (NRP1) (ENSMUSG00000025810)</i>	-2.26 (0.0154)	Positive and negative regulator of angiogenesis
19	<i>multimerin 2 (Mmrn2)</i> (ENSMUSG00000041445)	-2.27 (0.048801)	Negative regulator of angiogenesis
20	<i>connective tissue growth factor (Ctgf)</i> (ENSMUSG00000019997)	-2.28 (0.07594)	Involved in angiogenesis. Interacts with endothelial cells
21	<i>Metalloproteinase inhibitor 2 (TIMP2)</i> (ENSMUSG00000017466)	-2.38 (0.0049)	Positive regulation of angiogenesis in tumors
22	<i>Thrombospondin 1 (Thbs1)</i> (ENSMUSG00000040152)	-2.53 (0.0054)	Positive and negative regulator of angiogenesis
23	<i>collagen, type IV, alpha 2 (Col4a2)</i> (ENSMUSG00000031503)	-2.57 (0.0223)	Negative regulator of angiogenesis
24	<i>Platelet-derived growth factor receptor beta (PDGFRB) (ENSMUSG00000024620)</i>	-2.66 (0.0162)	Positive regulator of angiogenesis
25	<i>Angiopoietin-1 receptor (TEK)</i> (ENSMUSG00000006386)	-2.7 (0.015)	Positive and negative regulator of angiogenesis
26	<i>fibulin 5 (Fbln5) (ENSMUSG00000021186)</i>	-2.72 (0.0014)	Endogenous inhibitor of angiogenesis
27	<i>Receptor-type tyrosine-protein phosphatase beta (PTPRB)</i> (ENSMUSG00000020154)	-2.72 (0.011)	Positive and negative regulator of angiogenesis

28	<i>collagen, type IV, alpha 1 (Col4a1)</i> (ENSMUSG00000031502)	−2.76 (0.016)	Inhibits angiogenesis and tumor formation
29	<i>fibronectin 1 (Fn1)</i> (ENSMUSG00000026193)	−2.83 (0.0283)	Inhibits angiogenesis and tumor formation
30	<i>Platelet-derived growth factor receptor alpha (PDG-FRA)</i> (ENSMUSG00000029231)	−2.91 (0.0001)	Promoter of angiogenesis
31	<i>Pigment epithelium-derived factor (SERPINF1)</i> (ENSMUSG00000000753)	−2.92 (0.0171)	Potent inhibitor of angiogenesis
32	<i>Sushi repeat-containing protein SRPX2 (SRPX2)</i> (ENSMUSG00000031253)	−3.1 (0.033)	Positive and negative regulator of angiogenesis
33	<i>Thrombospondin 2 (Thbs2)</i> (ENSMUSG00000023885)	−3.24 (0.0078)	Negative regulator of angiogenesis
34	<i>Vasohibin-1 (VASH1)</i> (ENSMUSG00000021256)	−3.34 (0.0316)	Angiogenesis inhibitor
35	<i>Platelet-derived growth factor D (PDGFD)</i> (ENSMUSG00000032006)	−3.5 (0.014)	Positive regulator of angiogenesis
36	<i>Protocadherin-12 (PCDH12)</i> (ENSMUSG00000024440)	−3.58 (0.03)	PCDH12 is required for normal angiogenesis and is highly expressed in angiogenic endothelial cells
37	<i>matrix metalloproteinase 2 (Mmp2)</i> (ENSMUSG00000031740)	−4.27 (3.50E−05)	Positive and negative regulator of angiogenesis
38	<i>Coagulation factor XIII A chain (F13A1)</i> (ENSMUSG00000039109)	−4.39 (0.0000008)	Positive regulator of angiogenesis
39	<i>EGF-like repeats and discoidin I-like domains 3 (Edil3)</i> (ENSMUSG00000034488)	−4.41 (0.0235)	Promotes angiogenesis
40	<i>Angiopoietin-4 (ANGPT4)</i> (ENSMUSG00000027460)	−5.16 (0.0003)	Promotes endothelial cell survival, migration and angiogenesis
41	<i>Angiopoietin-1 (ANGPT1)</i> (ENSMUSG00000022309)	−7.01 (0.0006)	Activates or inhibits angiogenesis, depending on the context

Selected mouse genes from the down-regulated and up-regulated groups associated with angiogenesis. The proposed function indicated. For each gene, the gene symbol and name, fold change in expression and p-value are indicated. Negative numbers reflect down-regulation.

**Table S8.** VDAC1 silencing in a A549 lung cancer-derived tumor alters the expression of human ECM-related structural genes.

No	Gene Name (Ensembl)	Fold change si-hVDAC1/si-NT (P value)	Proposed Function
<b>ECM-related structural genes</b>			
1	<i>Laminin subunit gamma-3 (LAMC3)</i> (ENSMUSG00000043631)	7.46 (0.0061)	Structural molecule activity
2	<i>Laminin subunit alpha-1 (LAMA1)</i> (ENSG00000101680)	5.25 (0.0059)	ECM structural component
3	<i>Fibroleukin (FGL2)</i> (ENSG00000127951)	4.25 (0.0160)	ECM structural component
4	<i>Matrilin-3 (MATN3)</i> (ENSG00000132031)	−1.58 (0.0223)	Major component of cartilage and may play a role in the formation of extracellular filamentous networks
5	<i>Collagen alpha-2(V) chain (COL5A2)</i> (ENSMUSG00000030116)	−1.62 (0.0002)	Fibrillar-forming collagen
6	<i>Collagen alpha-1(V) chain (COL5A1)</i> (ENSG00000130635)	−1.67 (0.0001)	Fibrillar-forming collagen.
7	<i>Collagen alpha-1(XII) chain (COL12A1)</i> (ENSG00000111799)	−1.75 (0.0006)	ECM component conferring tensile strength
8	<i>Fibrillin-1 (FBN1)</i> (ENSG00000166147)	−1.83 (2.33E−05)	ECM component conferring elasticity
9	<i>Collagen alpha-2(IV) chain (COL4A2)</i> (ENSG00000134871)	−1.85 (0.0001)	ECM structural component
10	<i>Collagen alpha-1(IV) chain (COL4A1)</i> (ENSG00000187498)	−1.91 (4.09E−05)	ECM component conferring elasticity
11	<i>Collagen alpha-1(I) chain (COL1A1)</i> (ENSG00000108821)	−1.97 (0.0093)	Fibrillar-forming collagen
12	<i>Collagen alpha-2(I) chain (COL1A2)</i> (ENSG00000164692)	−2.09 (0.0153)	Fibrillar-forming collagen

13	Collagen alpha-1(VIII) chain (COL8A1) (ENSG00000144810)	−2.58 (0.0001)	Macromolecular component of the sub-endothelium
14	Collagen alpha-1(XI) chain (COL11A1) (ENSG00000060718)	−3.40 (0.0019)	Play an important role in fibrillogenesis by controlling lateral growth of collagen II fibrils
15	Collagen alpha-2(VIII) chain (COL8A2) (ENSG00000171812)	−4.53 (0.0001)	Macromolecular component of the sub-endothelium

Selected human genes from the down-regulated and up-regulated groups associated with extracellular matrix structure. The proposed function indicated. For each gene, the gene symbol and name, fold change in expression and p-value are indicated. Negative numbers reflect down-regulation.

**Table S9.** VDAC1 silencing in A549 lung cancer-derived tumors alters the expression of human ECM organization genes.

No	Gene Name (Ensembl)	Fold change si-hVDAC1/si-NT (P value)	Proposed Function
<b>ECM organization</b>			
1	Heparan sulfate glucosamine 3-O-sulfotransferase 2 (HS3ST2) (ENSG00000122254)	7.16 (0.0336)	Sulfotransferase
2	Inactive heparanase-2 (HPSE2) (ENSG00000172987)	5.73 (0.0077)	Binds heparin and heparan sulfate with high affinity but lacks heparanase activity. Inhibits HPSE
3	Stabilin-2 (STAB2) (ENSG00000136011)	5.03 (0.0443)	Phosphatidylserine receptor that enhances the engulfment of apoptotic cells. Hyaluronan receptor that binds to and mediates endocytosis of hyaluronic acid
4	LARGE xylosyl- and glucuronyltransferase 2 (GYLTL1B) (ENSG00000165905)	4.98 (0.0042)	Involved in protein glycosylation, a protein modification of ECM components necessary for ECM organization
5	Heparanase (HPSE) (ENSG00000173083)	3.34 (0.0022)	Participates in ECM degradation and remodeling
6	Type 2 lactosamine alpha-2,3-sialyltransferase (ST3GAL6) (ENSG00000064225)	2.69 (0.032)	Shows alpha-2,3-sialyltransferase activity toward Gal-beta(1,4)-GlcNAc on glycoproteins and glycolipids
7	Perlecan (heparan sulfate proteoglycan 2) (HSPG2) (ENSG00000142798)	−1.53 (0.0359)	An integral component of basement membranes where it is responsible for the fixed negative electrostatic charge and is involved in charge-selective ultrafiltration
8	Lactosylceramide 1,3-N-acetyl-beta-D-glucosaminyl- transferase (B3GNT5) (ENSG00000176597)	−1.63 (0.0364)	Plays a key role in the synthesis of lacto- or neolacto-series carbohydrate chains on glycolipids, notably by participating in the biosynthesis of HNK-1 and Lewis X carbohydrate structures
9	Carbohydrate sulfotransferase 11 (CHST11) (ENSG00000171310)	−1.64 (0.0186)	Catalyzes the transfer of sulfate to GalNAc position 4 in chondroitin
10	Lysyl oxidase (LOX) (ENSG00000113083)	−1.68 (0.0002)	Responsible for the post-translational oxidative deamination of peptidyl lysine residues in precursors to fibrous collagen and elastin
11	Coiled-coil domain-containing protein 80 (CCDC80) (ENSG00000091986)	−1.73 (2.3E−05)	Cell adhesion and matrix assembly
12	Lysyl oxidase-like 2 (LOXL2) (ENSG00000134013)	−1.79 (0.0155)	Promotes cross-linking of ECM proteins by mediating oxidative deamination of peptidyl lysine residues in precursors to fibrous collagen and elastin
13	FERM domain-containing protein 5 (FRMD5) (ENSG00000171877)	−1.80 0.0062	Regulates cell-matrix interactions via its interaction with ITGB5. Cell migration
14	Latent-transforming growth factor beta-binding protein 2 (Ltbp2) (ENSG00000119681)	−1.81 (0.0009)	Plays an integral structural role in elastic-fiber architectural organization and/or assembly
15	Mannose receptor C, type 2 (MRC2) (ENSMUSG00000020695)	−1.83 (0.0073)	Internalizes glycosylated ligands, remodeling and degradation of extracellular collagen matrices
16	Extracellular sulfatase Sulf-1 (SULF1) (ENSG00000137573)	−1.97 (0.0290)	Arylsulfatase activity and highly specific endoglucosamine-6-sulfatase activity. Removes sulfate from the C-6 position of glucosamine in heparin. Diminishes heparan sulfate proteoglycan sulfation
17	Biglycan (BGN) (ENSG00000182492)	−2.06 (0.0065)	Involved in collagen fiber assembly
18	Leucine-rich repeat-containing protein 15 (LRRC15) (ENSG00000172061)	−3.2 (0.0019)	ECM protein binding
19	Fibromodulin (FMOD) (ENSG00000122176)	−3.92 (0.0013)	Affects the rate of fibrils formation. May play a primary role in collagen fibrillogenesis
20	Cell migration-inducing and hyaluronan-binding protein (CE-MIP)(ENSMUSG00000030782)	−3.93 (1.63 × 10 <sup>−5</sup> )	Mediates depolymerization of hyaluronic acid via the cell membrane-associated clathrin-coated pit endocytic pathway. Binds to hyaluronic acid



Selected human genes from the down-regulated and up-regulated groups associated with extracellular matrix organization. The proposed function indicated. For each gene, the gene symbol and name, fold change in expression and p-value are indicated. Negative numbers reflect down-regulation.

**Table S10.** VDAC1 silencing in A549 lung cancer-derived tumors alters the expression of human ECM peptidases genes.

No	Gene Name (Ensembl)	Fold change si-hVDAC1/si-NT (P value)	Proposed Function
<b>ECM peptidases</b>			
1	<i>Macrophage metalloelastase (MMP12)</i> (ENSG00000262406)	13.19 (0.0004)	Metalloelastase
2	<i>Disintegrin and metallo-proteinase domain-containing protein 33 (ADAM33)</i> (ENSG00000149451)	5.92 (0.0063)	Metalloproteinase
3	<i>Dipeptidase 2 (DPEP2)</i> (ENSG00000167261)	4.31 (0.028)	Probable metalloprotease which hydrolyzes leukotriene D4 into leukotriene E4.
4	<i>Pappalysin-1 (PAPPA)</i> (ENSG00000182752)	-1.57 (0.0182)	Metalloproteinase which specifically cleaves IGFBP-4 and IGFBP-5, resulting in release of bound IGF
5	<i>A disintegrin and metalloproteinase with thrombospondin motifs 15</i> (ADAMTS15)(ENSG00000166106)	-1.95 (0.0068)	Metalloproteinase
6	<i>A disintegrin and metalloproteinase with thrombospondin motifs 4</i> (ADAMTS4)(ENSG00000158859)	-1.97 (0.0185)	Metalloproteinase
7	<i>72 kDa type IV collagenase (MMP2)</i> (ENSG00000087245)	-2.09 (0.0053)	Collagenase
8	<i>A disintegrin and metalloproteinase with thrombospondin motifs 7</i> (ADAMTS7)(ENSG00000136378)	-2.17 (0.0019)	Metalloproteinase
9	<i>Disintegrin and metalloproteinase domain-containing protein 19 (ADAM19)</i> (ENSG00000135074)	-2.30 (0.0045)	Protease
10	<i>Collagenase 3 (MMP13)</i> (ENSG00000137745)	-2.45 (0.0041)	Collagenase
11	<i>A disintegrin and metalloproteinase with thrombospondin motifs 12 (ADAMTS12)</i> (ENSG00000151388)	-3.93 (0.0012)	Metalloproteinase
12	<i>Matrix metalloproteinase-16 (MMP16)</i> (ENSG00000156103)	-3.96 ( $2.98 \times 10^{-6}$ )	Metalloproteinase

Selected human genes from the down-regulated and up-regulated groups associated with extracellular matrix peptidases. The proposed function indicated. For each gene, the gene symbol and name, fold change in expression and p-value are indicated. Negative numbers reflect down-regulation.

**Table S11.** VDAC1 silencing in a A549 lung cancer-derived tumor alters the expression of human intercellular-interaction-associated genes.

No	Gene Name (Ensembl)	Fold change si-hVDAC1/si-NT (P value)	Proposed Function
<b>Human intercellular-interaction-associated genes</b>			
1	<i>Cadherin-3 (CDH3)</i> (ENSG00000062038)	7.61 (0.0004)	Calcium-dependent cell adhesion protein
2	<i>Down syndrome cell adhesion molecule (DSCAM)</i> (ENSG00000171587)	5.69 (0.043)	Mediates intracellular signaling by stimulating the activation of MAPK8 and MAP kinase p38. Adhesion molecule that promotes lamina-specific synaptic connections in the retina
3	<i>Protocadherin-7 (PCDH7)</i> (ENSG00000169851)	5.03 (0.004)	Homophilic cell adhesion via plasma membrane adhesion molecules. Platelet degranulation
4	<i>Tyrosine-protein kinase Mer (MERTK)</i> (ENSG00000153208)	4.31 (0.008)	Plays a role in various processes, such as macrophage clearance of apoptotic cells, platelet aggregation, cytoskeleton reorganization and engulfment. Induces production of suppressors of cytokine signaling SOCS1 and SOCS3

5	<i>Homeobox protein DLX-1 (DLX1)</i> (ENSG00000144355)	3.26 (0.034)	Inhibits several cytokine signaling pathways, such as TGFB1, activin-A/INHBA and BMP4 by interfering with the transcriptional stimulatory activity of transcription factors, such as MSX2, FAST2, SMAD2 and SMAD3 during hematopoietic cell differentiation
6	<i>Fermitin family homolog 3 (FERMT3)</i> (ENSG00000149781)	2.43 (0.011)	Plays a central role in cell adhesion. Required for activation of integrin beta-2 in polymorphonuclear granulocytes
7	<i>Armadillo repeat protein deleted in velo-cardio-facial syndrome (ARVCF)</i> (ENSG00000099889)	2.4 (0.033)	Involved in protein-protein interactions at adherens junctions
8	<i>Desmoplakin (DSP)</i> (ENSG00000096696)	2.24 (0.033)	Major high molecular weight protein of desmosomes. Involved in the organization of the desmosomal cadherin-plakoglobin complexes into discrete plasma membrane domains and in the anchoring of intermediate filaments to the desmosomes
9	<i>Arf-GAP with coiled-coil, ANK repeat and PH domain-containing protein 1 (ACAP1)</i> (ENSG00000072818)	1.79 (0.0007)	Required for regulated export of ITGB1 from recycling endosomes to the cell surface and ITGB1-dependent cell migration
10	<i>N-acetylneuraminase lyase (NPL)</i> (ENSG00000135838)	1.63 (0.045)	Catalyzes the cleavage of N-acetylneuraminic acid to form pyruvate and N-acetylmannosamine. Prevents sialic acids from being recycled to the cell surface
11	<i>Arylsulfatase J (ARSJ)</i> (ENSG00000180801)	-1.51 (0.023)	Glycosphingolipid metabolic process, post-translational protein modification
12	<i>Blood vessel epicardial substance (BVES)</i> (ENSG000000112276)	-1.55 (0.0151)	Cell adhesion molecule involved in the establishment and/or maintenance of cell integrity. Involved in the formation and regulation of the tight junction paracellular permeability barriers in epithelial cells
13	<i>Discoidin, CUB and LCCL domain-containing protein 2 (DCBLD2)</i> (ENSG00000057019)	-1.55 (0.027)	Negative regulator of cell growth
14	<i>Pleckstrin homology-like domain family B member 2 (PHLDB2)</i> (ENSG00000144824)	-1.56 (0.0044)	Cadherin binding
15	<i>Sushi, von Willebrand factor type A, EGF and pentraxin domain-containing protein 1 (SVEP1)</i> (ENSG00000165124)	-1.64 (0.0157)	Plays a role in the cell attachment process
16	<i>Protein NOV homolog (NOV)</i> (ENSG000000136999)	-1.68 (0.0397)	Fibroblast adhesion through ITGA5:ITGB1 and ITGA6:ITGB1 and induces fibroblast chemotaxis through ITGA5:ITGB5
17	<i>Anthrax toxin receptor 1 (ANTXR1)</i> (ENSG00000169604)	-1.70 (0.0470)	Cell attachment via collagen 1 and gelatin, migration. Interacts with ECM proteins
18	<i>Cadherin-4 (CDH4)</i> (ENSG00000179242)	-1.73 (0.0483)	Cell adhesion protein
19	<i>Cadherin-2 (CDH2)</i> (NCAD) (ENSG00000170558)	-1.76 (0.0057)	Cell adhesion protein
20	<i>Cadherin-5 (CDH5)</i> (ENSG00000179776)	-2.36 (0.0134)	Cell adhesion protein
21	<i>Probable carboxypeptidase X1 (CPXM1)</i> (ENSG00000088882)	-2.76 (0.0025)	May be involved in cell-cell interactions
22	<i>Integrin alpha-D (ITGAD)</i> (ENSG00000156886)	4.33 (0.0050)	Alpha subunit of the cell surface heterodimer. Involved in the activation and adhesion functions of leukocytes
23	<i>Integrin beta (ITGB2)</i> (ENSG00000160255)	3.03 (0.0020)	Receptor for ICAM1, ICAM2, ICAM3 and ICAM4
24	<i>Integrin alpha-IIb (ITGA2B)</i> (ENSG00000005961)	2.69 (0.0263)	Receptor for fibronectin, fibrinogen, plasminogen, prothrombin, thrombospondin and vitronectin
25	<i>Integrin beta-like protein 1 (ITGBL1)</i> (ENSG00000198542)	-2.35 (0.0416)	Cell adhesion protein
26	<i>Integrin alpha-11 (ITGA11)</i> (ENSG00000137809)	-2.61 (0.0018)	Receptor for collagen
27	<i>Integrin binding sialoprotein (IBSP)</i> (ENSG00000029559)	-10.73 (0.0110)	Appears to form an integral part of the mineralized matrix. Probably important for cell-matrix interaction
28	<i>Intercellular adhesion molecule 5 (ICAM5)</i> (ENSG00000105376)	5.48 (0.0054)	Integrin binding
29	<i>Neuronal cell adhesion molecule (NRCAM)</i> (ENSG00000091129)	-2.55 (0.0072)	Cell adhesion protein that is required for normal responses to cell-cell contacts in brain and the peripheral nervous system
30	<i>Claudin-11 (CLDN11)</i> (ENSG0000013297)	2.35 (0.0463)	Plays a major role in tight junction-specific obliteration of the intercellular space

31	<i>Chymotrypsin-like elastase family member 1 (CELA1) (ENSG00000139610)</i>	−4.06 (0.0447)	Acts on elastin
32	<i>Endomucin (EMCN) (ENSG00000164035)</i>	−7.95 (0.0236)	Interferes with the assembly of focal adhesion complexes and inhibits interaction between cells and the ECM
33	<i>Insulin growth factor-like family member 2 (IGFL2) (ENSG00000204866)</i>	−4.17 (0.0011)	Potential ligand of the IGFLR1 cell membrane receptor

Selected human genes from the down-regulated and up-regulated groups associated with intercellular-interaction. The proposed function indicated. For each gene, the gene symbol and name, fold change in expression and p-value are indicated. Negative numbers reflect down-regulation.

**Table S12.** VDAC1 silencing in a A549 lung cancer-derived tumor alters the expression of human angiogenesis-associated genes.

No	Gene Name (Ensembl)	Fold change si-hVDAC1/si-NT (P value)	Proposed Function
<b>Angiogenesis</b>			
1	<i>Ectonucleotide pyrophosphatase/phosphodiesterase family member 2 (ENPP2) (ENSG00000136960)</i>	16.69 (0.00001)	Acts as an angiogenic factor by stimulating migration of smooth muscle cells and microtubule formation. Stimulates migration of melanoma cells, probably via a pertussis toxin-sensitive G protein. May play a role in induction of parturition. Possible involvement in cell proliferation and adipose tissue development. Tumor cell motility-stimulating factor
2	<i>Receptor-type tyrosine-protein kinase FLT3 (FLT3) (ENSG00000122025)</i>	10.96 (0.0056)	Activated receptor kinase subsequently phosphorylates and activates multiple cytoplasmic effector molecules in pathways involved in apoptosis, proliferation, and differentiation of hematopoietic cells in bone marrow. Mutations that result in the constitutive activation of this receptor result in acute myeloid leukemia and acute lymphoblastic leukemia
3	<i>Phosphoinositide 3-kinase regulatory subunit 6 (PIK3R6) (ENSG00000276231)</i>	4.82 (0.024)	Positive angiogenesis regulation. Regulatory subunit of the PI3K
4	<i>Filamin A-interacting protein 1-like (FILP1L) (ENSG00000168386)</i>	4.75 (0.0027)	Acts as a regulator of anti-angiogenic activity on endothelial cells. When over-expressed in endothelial cells, leads to inhibition of cell proliferation and migration and increased apoptosis. Inhibits melanoma growth when expressed in tumor-associated vasculature
5	<i>Secretogranin-2 (SCG2) (ENSG00000171951)</i>	4.52 (0.018)	Neuroendocrine secretory granule protein. Precursor for biologically active peptides. Positive regulator of angiogenesis
6	<i>Sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain (semaphorin) 4A (SEMA4A) (ENSMUSG00000028064)</i>	3.9 (0.014)	Negative regulator of angiogenesis
7	<i>Ephrin-A3 (EFNA3) (ENSG00000143590)</i>	2.21 (0.04)	Negative regulator of angiogenesis
8	<i>Ras-interacting protein 1 (RASIP1) (ENSG00000105538)</i>	2.18 (0.041)	Required for proper formation of vascular structures that develop via both vasculogenesis and angiogenesis. Acts as a critical and vascular-specific regulator of GTPase signaling, cell architecture, and adhesion, which is essential for endothelial cell morphogenesis and blood vessel tubulogenesis
9	<i>Guanine nucleotide exchange factor VAV3 (VAV3) (ENSG00000134215)</i>	2 (0.018)	Plays an important role in angiogenesis
10	<i>Angio-associated migratory cell protein (AAMP) (ENSG00000127837)</i>	1.51 (0.0214)	Member of the immunoglobulin superfamily. Associated with angiogenesis, with potential roles in endothelial tube formation and migration of endothelial cells
11	<i>Platelet-derived growth factor C (PDGFC) (ENSG00000145431)</i>	−1.68 (0.0007)	Pro-angiogenic factor
12	<i>Platelet-derived growth factor receptor beta (PDGFRB) (ENSG00000113721)</i>	−1.72 (0.0130)	Pro-angiogenic factor
13	<i>R-spondin-3 (RSPO3) (ENSG00000146374)</i>	−1.84 (0.0331)	Activator of the Wnt signaling pathway by acting as a ligand for LGR4–6 receptors, key regulators of angiogenesis
14	<i>Sushi repeat-containing protein SRPX2 (SRPX2) (ENSG00000102359)</i>	−2.14 (0.0143)	Plays a positive role in angiogenesis by inducing endothelial cell migration and the formation of vascular network (cords). Involved in cellular migration and adhesion
15	<i>Hedgehog-interacting protein (HHIP) (ENSG00000164161)</i>	−2.21 (0.0168)	Negative regulation of angiogenesis

16	<i>UPF0606 protein KIAA1549L</i> (KIAA1549L) (ENSG00000110427)	−2.71 (0.0100)	Development VEGF signaling via VEGFR2-generic cascades. Angiogenesis
17	<i>Apelin receptor (APLNR)</i> (ENSG00000134817)	−2.76 (0.0197)	Pro-angiogenic factor

Selected human genes from the down-regulated and up-regulated groups associated with angiogenesis. The proposed function indicated. For each gene, the gene symbol and name, fold change in expression and p-value are indicated. Negative numbers reflect down-regulation.

**Table S13.** VDAC1 silencing in a A549 lung cancer-derived tumor alters the expression of human growth factor genes.

No	Gene Name (Ensembl)	Fold change si-hVDAC1/si-NT (P value)	Proposed Function
<b>Growth factors</b>			
1	<i>Fibroblast growth factor 5 (FGF5)</i> (ENSG00000138675)	11.88 (0.0088)	Plays important role in regulating cell proliferation and cell differentiation
2	<i>Fibroblast growth factor 8 (FGF8)</i> (ENSG00000107831)	4.78 (0.0019)	Plays an important role in regulating embryonic development, cell proliferation, cell differentiation and cell migration
3	<i>Transforming growth factor-beta-induced protein ig-h3 (TGFB1)</i> (ENSG00000120708)	−1.61 (0.0276)	Plays a role in cell adhesion. May play a role in cell-collagen interactions, angiogenesis
4	<i>Fibroblast growth factor 12 (FGF12)</i> (ENSG00000114279)	−1.68 (0.0198)	Involved in the positive regulation of voltage-gated sodium channel activity
5	<i>Transforming growth factor, beta 2</i> (TGFB2) (ENSG00000092969)	−2.03 (1.52E−07)	Has suppressive effects on interleukin-2-dependent T-cell growth.
6	<i>Insulin growth factor-like family member 1</i> (IGFL1) (ENSG00000188293)	−2.94 (0.0037)	Probable ligand of the IGFLR1 cell membrane receptor
7	<i>Insulin growth factor-like family member 2</i> (IGFL2) (ENSG00000204866)	−4.17 (0.0011)	Potential ligand of the IGFLR1 cell membrane receptor

Selected human genes from the down-regulated and up-regulated groups associated with growth factors. The proposed function indicated. For each gene, the gene symbol and name, fold change in expression and p-value are indicated. Negative numbers reflect down-regulation.

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