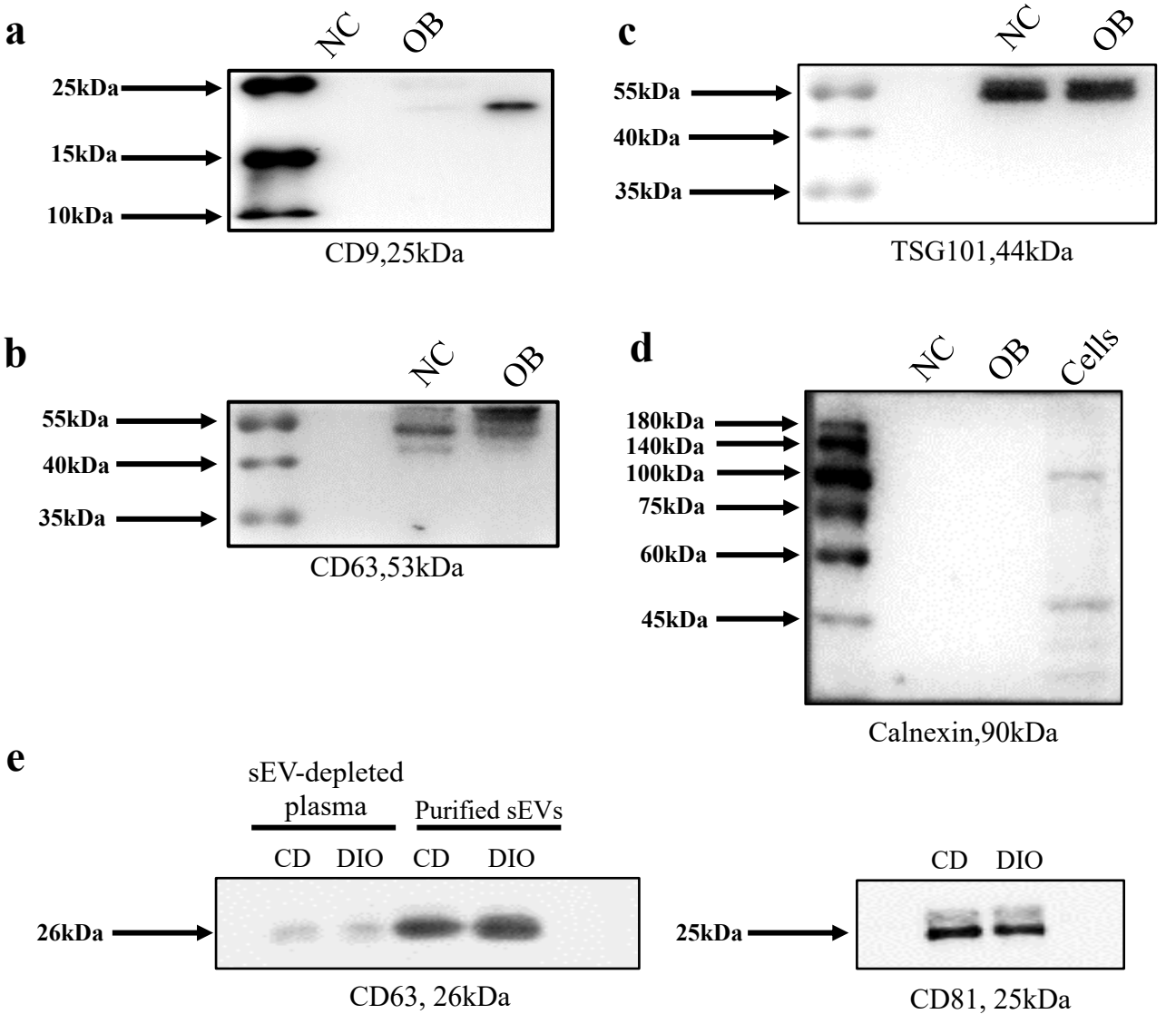
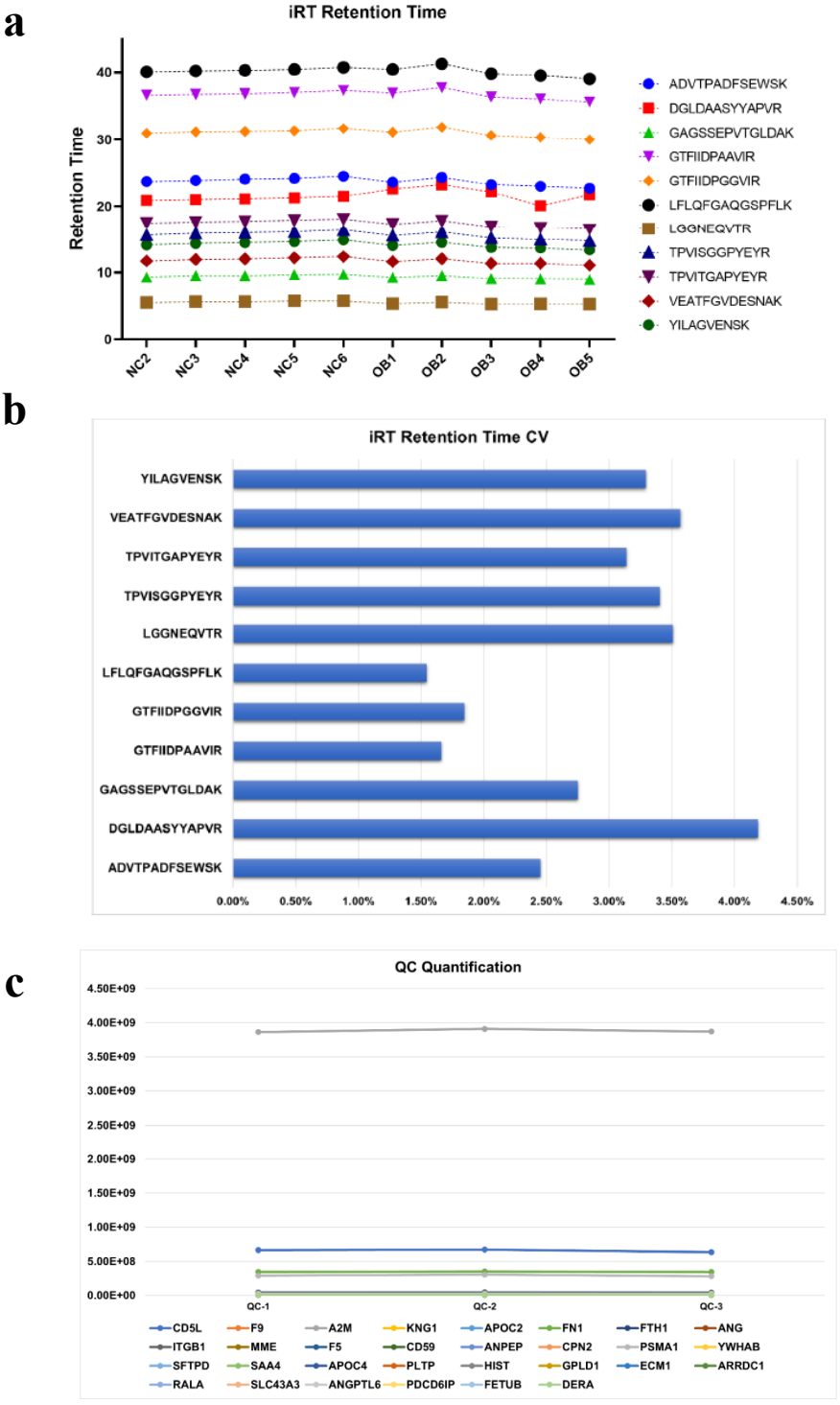
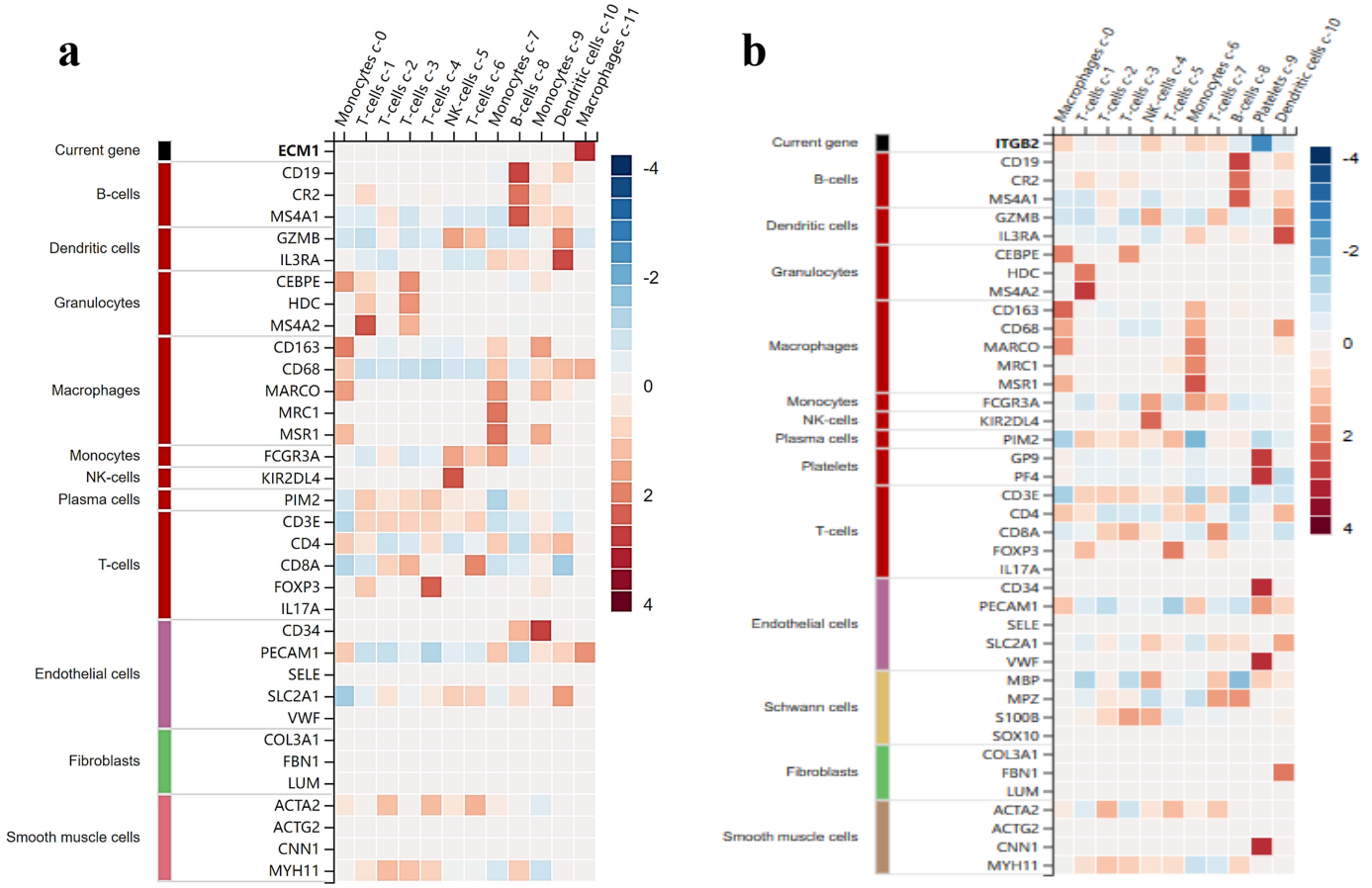


Supplementary Figure S1
Representative Western blots showing the expressions of sEV markers
sEV markers in the circulating sEVs purified from the plasma of human subjects **(a)** CD9, **(b)** CD63, **(c)** TSG101, **(d)** calnexin. **(e)** Expressions of sEV markers CD63 and CD81 in the circulating sEVs purified from the plasma of mouse models. NC, normal weight healthy human subjects; OB, human subjects with obesity or overweight; CD, control diet fed mice; DIO, high-fat diet-induced obesity mice; cells, cell sample is included as positive control.

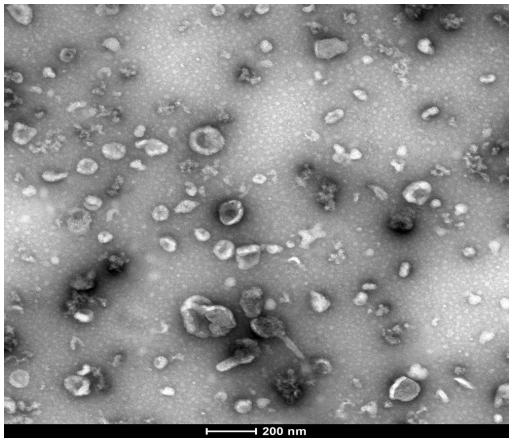


Supplementary Figure S2
Quality control tests for MRM-mass spectrometry
(a) iRT retention time and **(b)** iRT retention time CV of the sample peptide in the MRM-mass spectrometry that indicate the qualitative stability of the repeated tests and small systemic errors of the samples. **(c)** The quantitative results of the detected proteins in the quality control (QC) samples.



Supplementary Figure S3
Expressions of EMC1 and ITGB2 in macrophages
Single cell sequencing analysis showing **(a)** ECM1 expressions in peripheral blood mononuclear cells (PBMC) including macrophages, **(b)** ITGB2 (integrin-β2) expressions in PBMC including macrophages.

a



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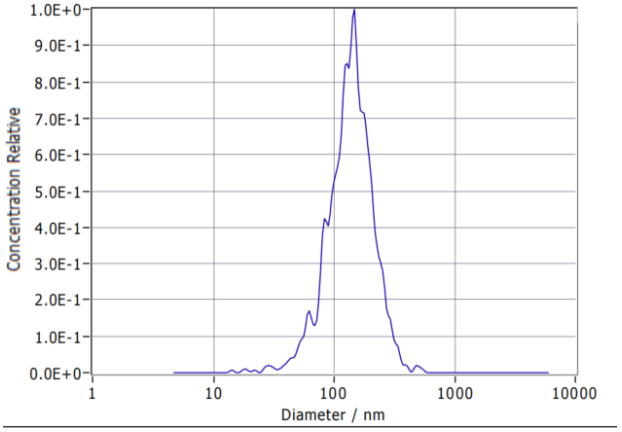
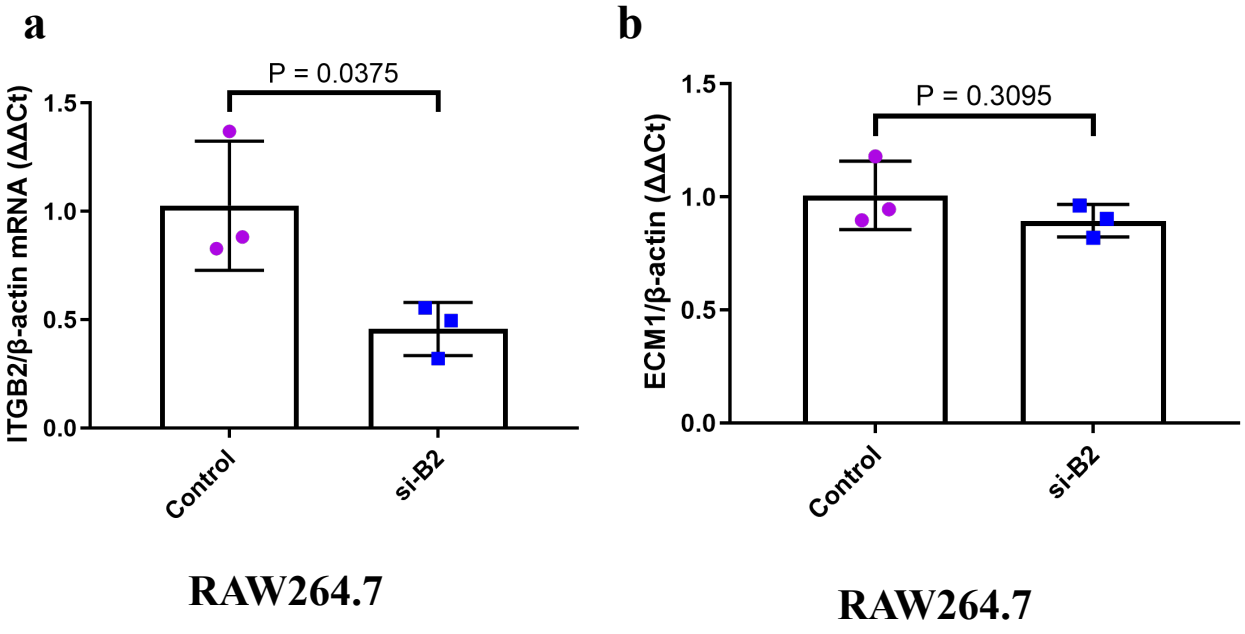
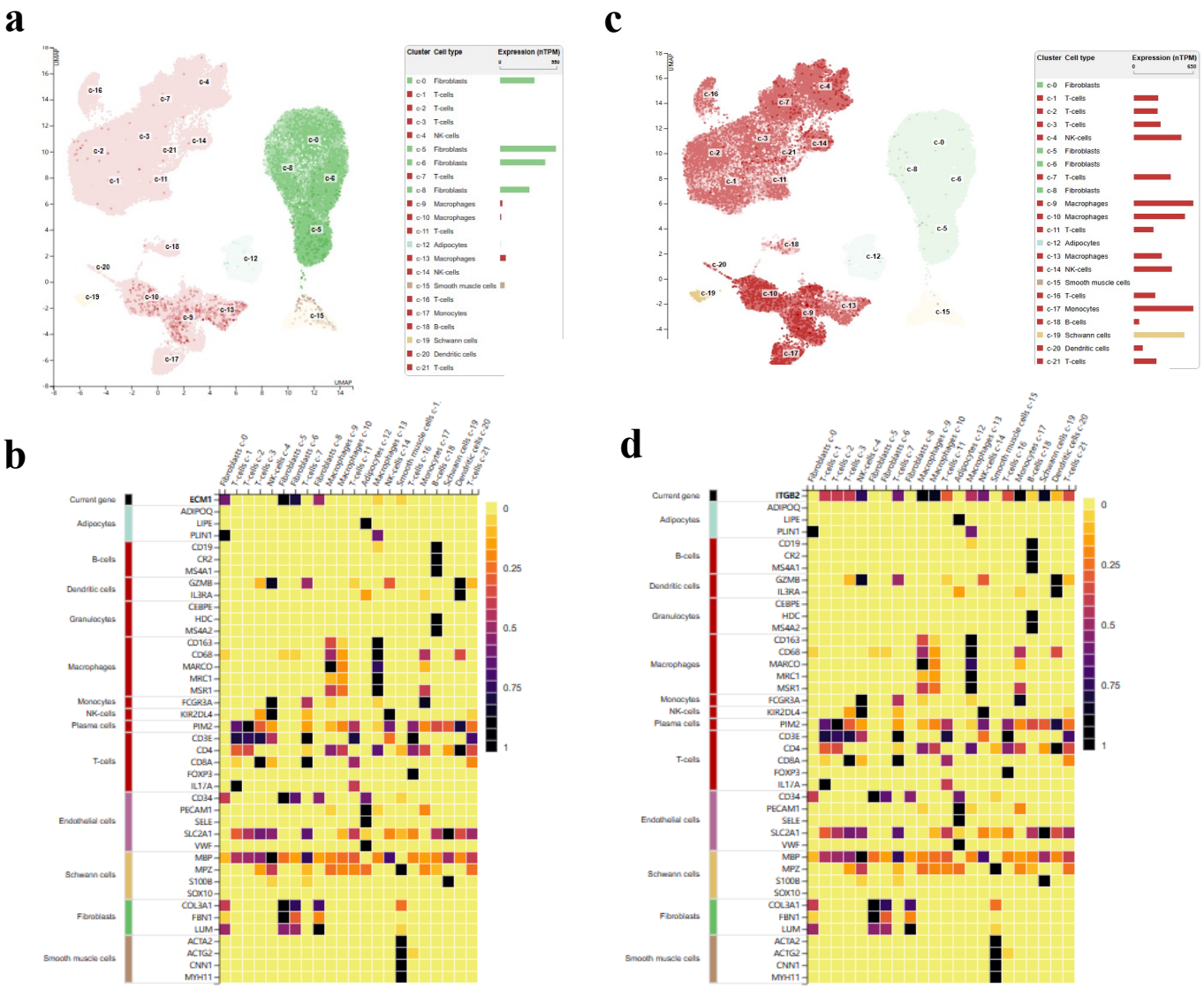


Supplementary Figure S4
sEVs released by RAW264.7 cells
(a) Transmission electron microscopy (TEM) and **(b)** nanoparticle tracking analysis (NTA) of the sEVs released by RAW264.7 cells.

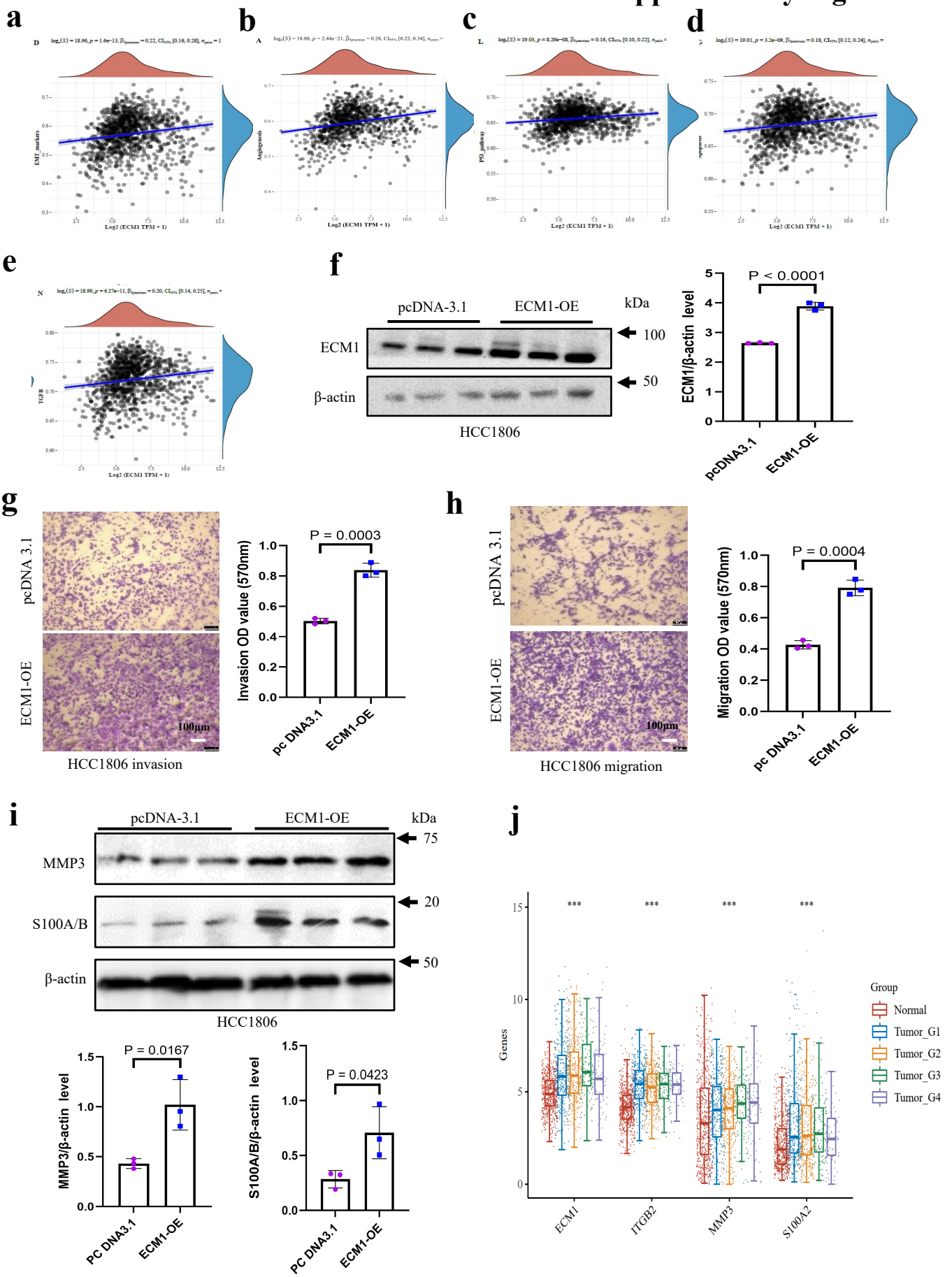


Supplementary Figure S5
ITGB2 and ECM1 mRNA levels in integrin-β2-knockdown and control RAW264.7 cells
(a) ITGB2 and **(b)** ECM1 mRNA levels in the integrin-β2-knockdown and control RAW264.7 cells. n=3 individual experiments; two-sided unpaired *t*-test for (**a, b**); p values are indicated in graphs. si-β2, integrin-β2-knockdown cells; NC, control cells. Source data are provided as a Source Data file.



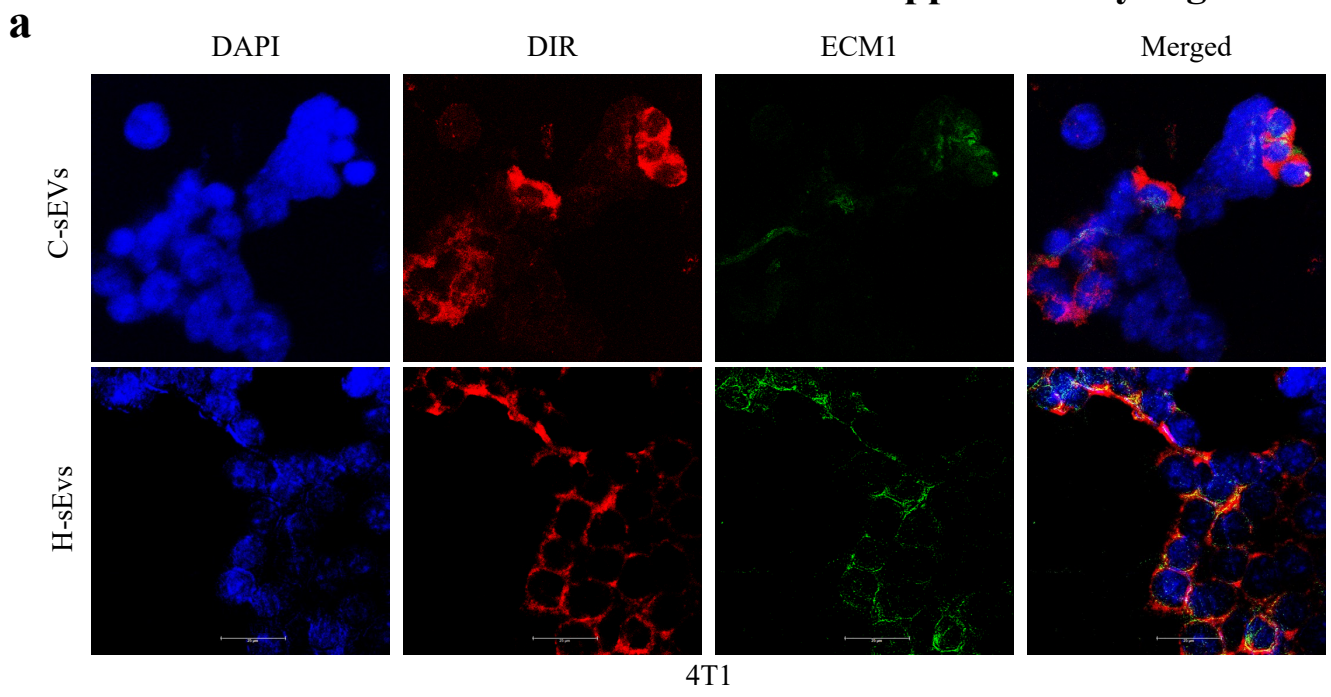
Supplementary Figure S6
Expressions of ECM1 and integrin-β2 in adipose tissues
Single cell sequencing analysis showing **(a-b)** ECM1 expression in adipose tissues, **(c-d)** integrin-β2 expression in adipose tissues.

Supplementary Figure S7



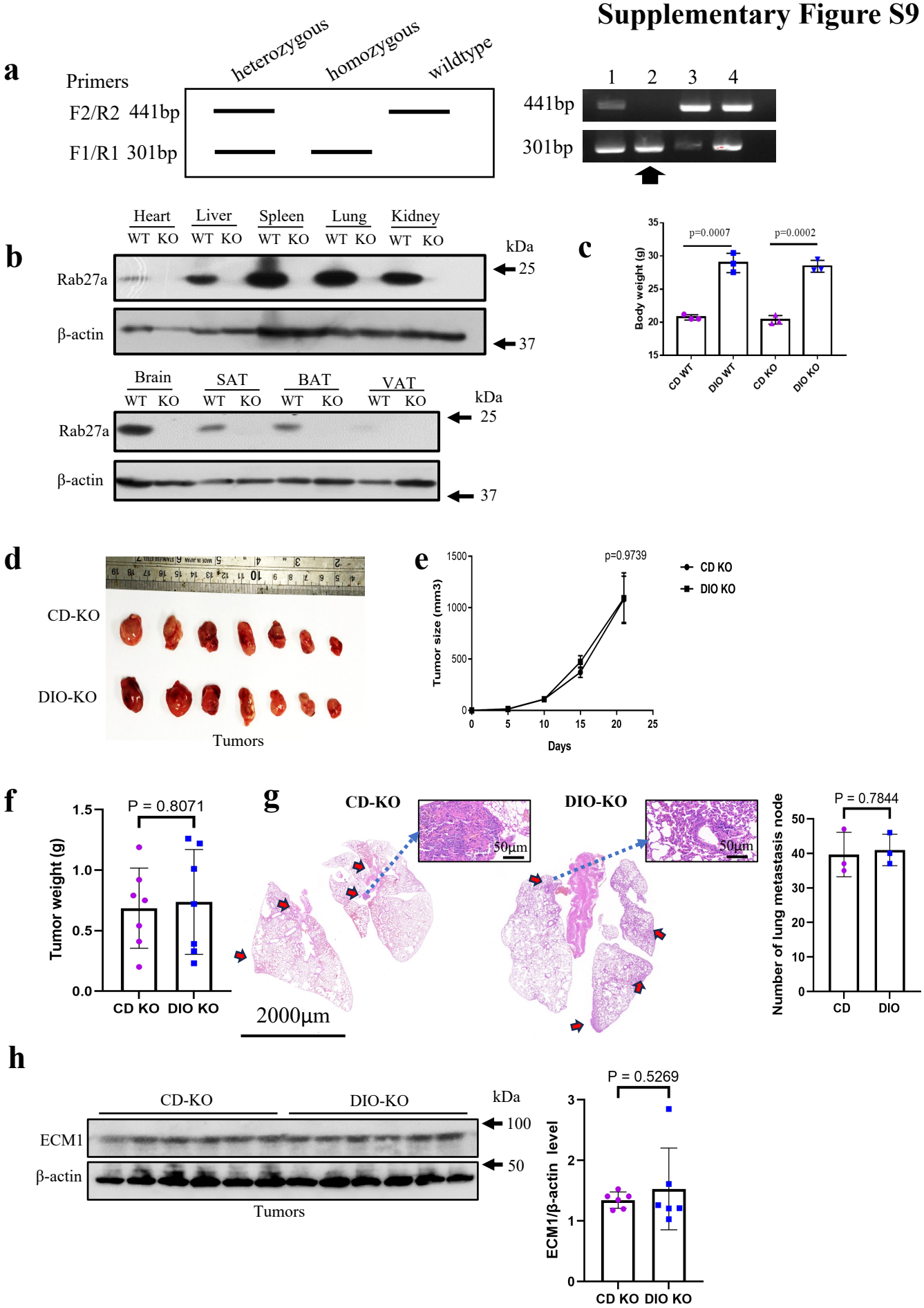
Supplementary Figure S7
Overexpression of ECM1 increases MMP3 and S100A/B expressions and metastatic potential of BC cells
Virtual Flow analysis showing the correlation between ECM1 and oncogenic signaling pathway scores in human breast cancer **(a)** epithelial-mesenchymal-transition (EMT) markers, **(b)** angiogenesis, **(c)** P53, **(d)** apoptosis and **(e)** transforming growth factor beta (TGF-beta). **(f)** ECM1 protein levels in ECM1-overexpressed (ECM1-OE) and empty vector (pcDNA-3.1)-transfected human breast cancer cells HCC1806. **(g)** Invasion and **(h)** migration of the ECM1-overexpressed and control HCC1806 cells. **(i)** Expressions of MMP3 and S100A/B in the ECM1-overexpressed and empty vector-transfected HCC1806 cells. **(j)** Prognosis analysis showing the correlations between the expressions of ECM1, MMP3, VEGF and S100A2 in 898 breast cancer patients who were divided into 4 stages, including G 1(N=333), G 2 (N=366), G 3 (N=120), G 4 (N=79). A total of 572 normal tissues (N=113 para-cancer tissue from TCGA database; N=459 from Genotype-Tissue Expression database) were included as controls. MMP3, matrix metallopeptidase 3; VEGF, vascular endothelial growth factor; ECM1, extracellular matrix protein 1. Shown is the mean ± SD; n = 3 independent experiments; two-sided unpaired *t*-test for (**f-i**); The Kruskal-Wallis test with the Wilcoxon's multiple comparison for (j); p values are indicated in graphs. Source data are provided as a Source Data file.

Supplementary Figure S8



Supplementary Figure S8
sEVs treatments in 4T1 cells
(a) Expression of ECM1 protein in sEVs-treated 4T1 cells shown by immunofluorescence staining. (**b)** Expressions of ECM1, MMP3 and S100A/B proteins in sEVs-treated 4T1 cells. **(c)** Expression of ECM1 mRNA levels in the sEVs-treated 4T1 cells. **(d)** Invasion and migration of sEVs-treated 4T1 cells. Shown is the mean ± SD; n = 3 independent experiments; two-sided unpaired *t*-test for (**a-d**); p values are indicated in graphs. C-sEVs, circulating sEVs in CD mice; H-sEVs, circulating sEVs in high fat diet-feeding mice; ECM1, extracellular matrix protein 1; MMP3, matrix metallopeptidase 3. Source data are provided as a Source Data file.

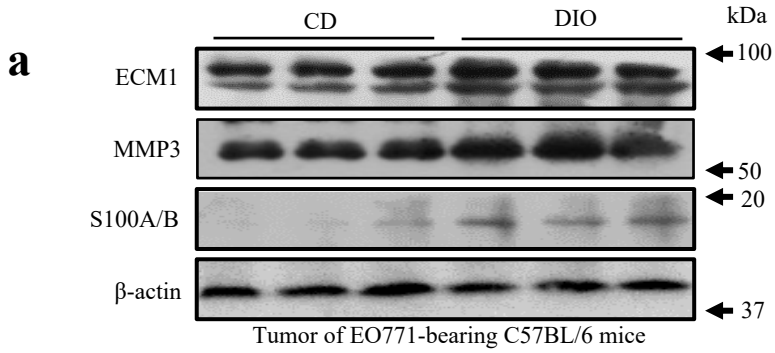
Supplementary Figure S9

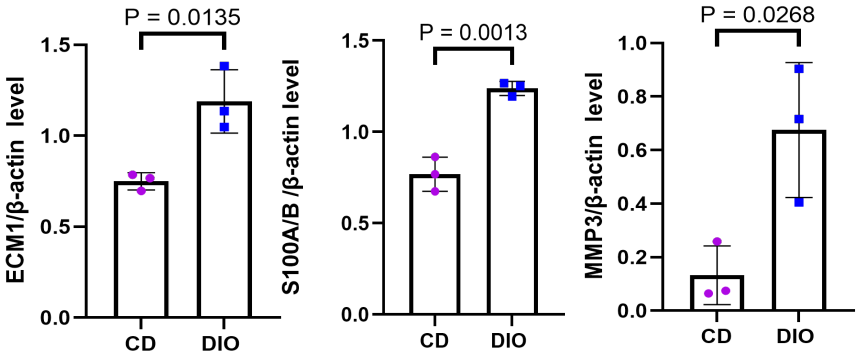


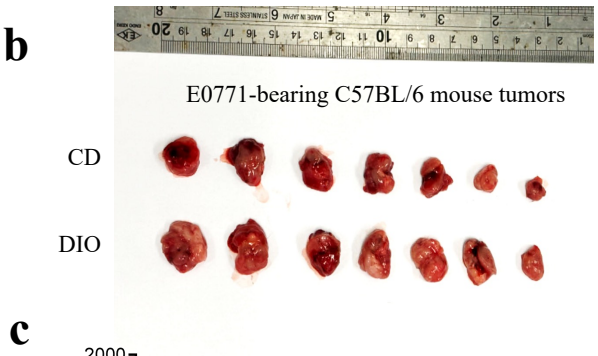
Supplementary Figure S9
Obesity fails to increase breast cancer growth and metastasis in Rab27a knockout mouse model

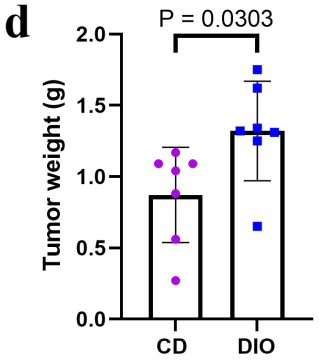
(a) Genotyping of B6/J-Rab27a-Cas9-KO mice and **(b)** Rab27a protein expressions in the heart, liver, spleen, lung, kidney, brain, subcutaneous adipose tissue (SAT), epididymal adipose tissues (EAT) and visceral adipose tissue (VAT) of the B6/J-Rab27a-Cas9-KO (KO) mice. **(c)** Establish DIO mouse model with the B6/J-Rab27a-Cas9-KO mice and isogenic mice. **(d)** Tumors, **(e)** tumor size, **(f)** tumor weight, **(g)** lung metastasis and **(h)** tumor ECM1 protein levels in the mouse models. Mouse tumor sizes are presented as the mean ± SEM; other data are presented as mean ± SD; two-sided unpaired *t*-test for (**d-h**); n = 7 mice in each group; p values are indicated in graphs. WT, wildtype; KO, B6/J-Rab27a-Cas9-KO mice; CD-KO, control diet fed B6/J-Rab27a-Cas9-KO mice; DIO-KO, high fat diet induced obesity B6/J-Rab27a-Cas9-KO mice; ECM1, extracellular matrix protein 1. Source data are provided as a Source Data file.

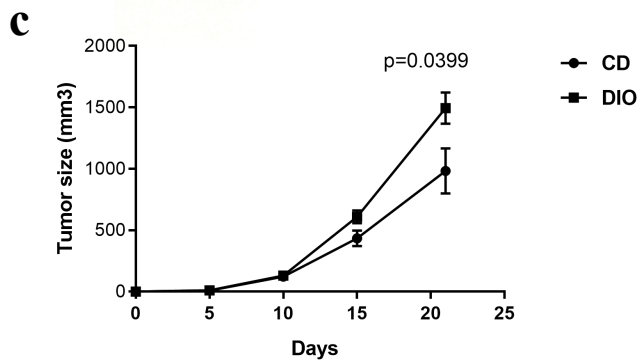
Supplementary Figure S10

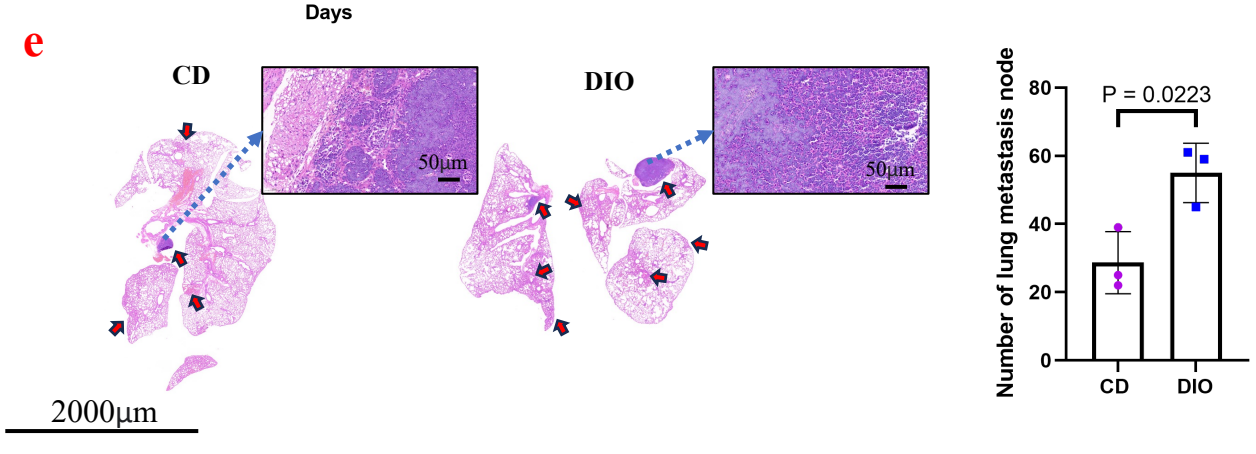










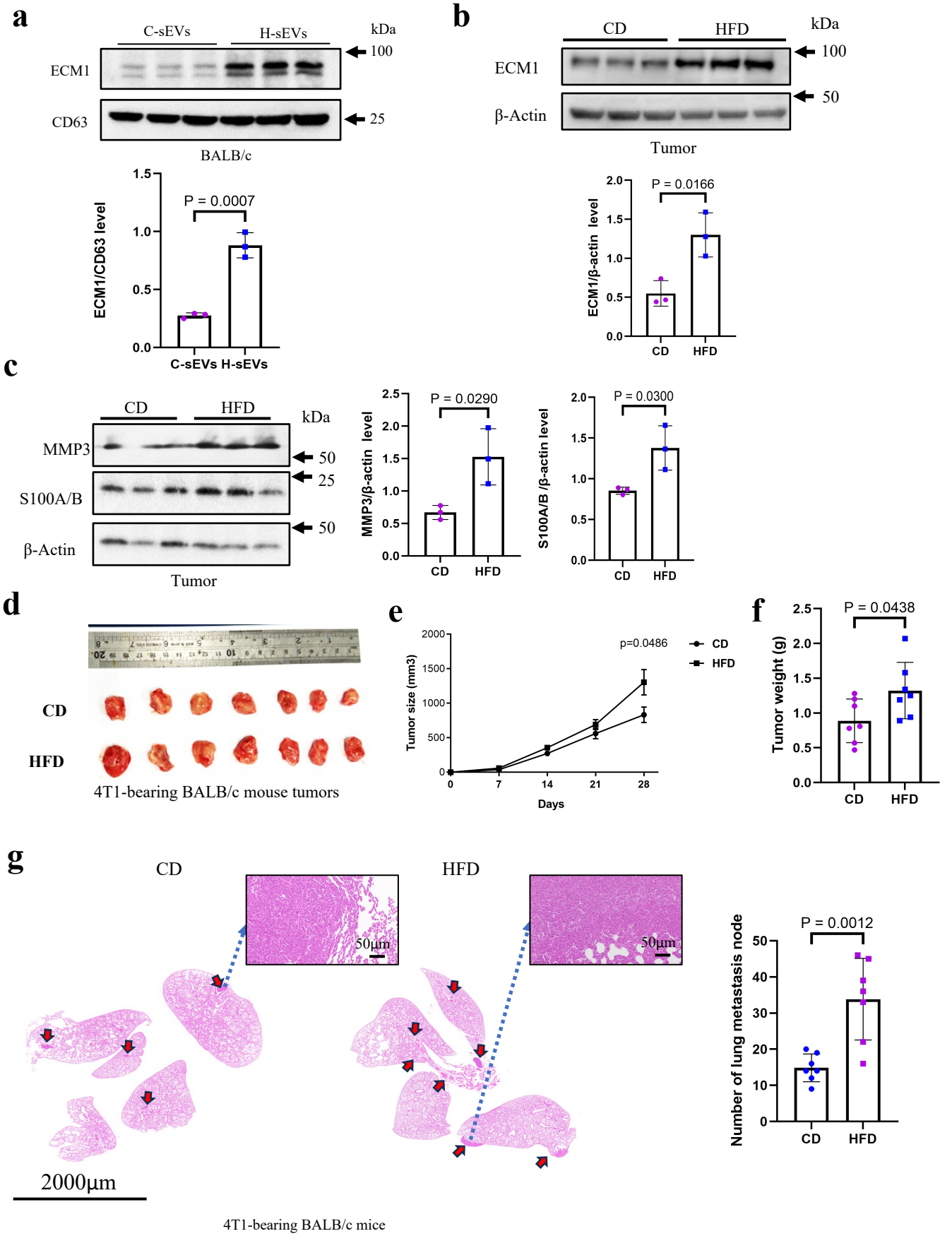


Supplementary Figure S10

Obesity increases breast cancer growth and metastasis in E0771-bearing C57BL/6 mice

(a) Protein expressions of ECM1, MMP3 and S100A/B in the tumors of the E0771-bearing CD and DIO mice. **(b)** Tumors, **(c)** tumor size, **(d)** tumor weight and **(e)** lung metastasis of the E0771-bearing CD and DIO mice. Mouse tumor sizes are presented as the mean ± SEM, other data are presented as mean ± SD; all two-sided unpaired *t*-test; n = 7 mice in each group, p values are indicated in graphs. ECM1, extracellular matrix protein 1; MMP3, matrix metallopeptidase 3; CD, control diet; DIO, high fat diet induced obesity. Source data are provided as a Source Data file.

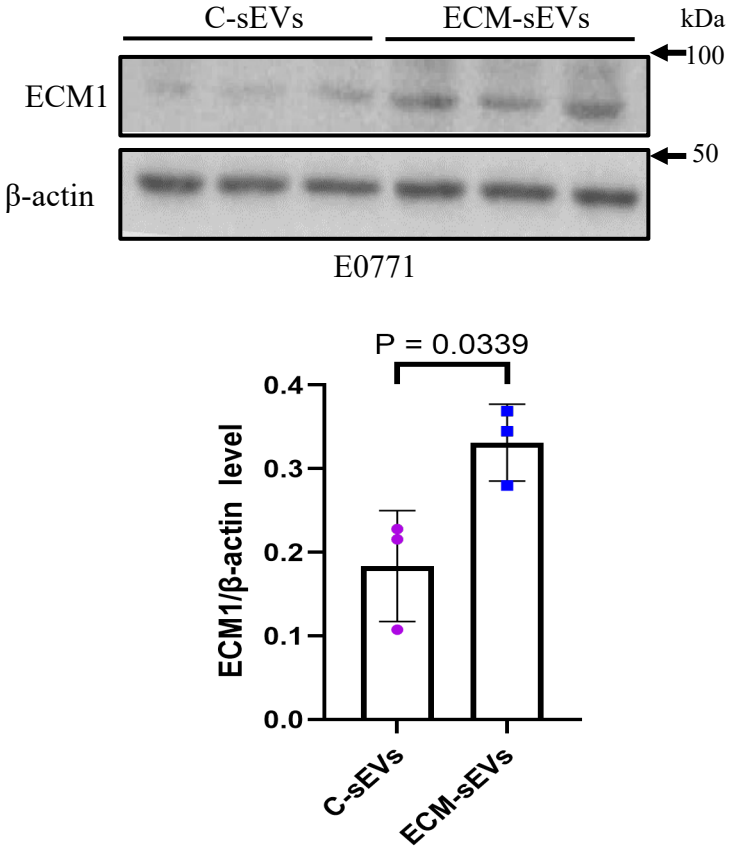
Supplementary Figure S11



Supplementary Figure S11

Obesity increases breast cancer growth and metastasis in 4T1-bearing BALB/c mice

(a) ECM1 protein levels in the circulating sEVs of CD mice (C-sEVs) and HFD mice (H- sEVs). Protein expressions of **(b)** ECM1 and **(c)** MMP3 and S100A/B in the tumors of the 4T1-bearing BALB/c mice after dietary intervention. **(d)** Tumors, **(e)** tumor size, **(f)** tumor weight and **(g)** lung metastasis of the 4T1-bearing BALB/c mice after dietary intervention. Mouse tumor sizes are presented as the mean ± SEM; other data are presented as mean ± SD; all two-sided unpaired *t*-test; n = 7 mice in each group, p values are indicated in graphs. ECM1, extracellular matrix protein 1; MMP3, matrix metallopeptidase 3; CD, control diet; HFD, high fat diet. Source data are provided as a Source Data file.



Supplementary Figure S12
Treatments with ECM1 construct-loaded sEVs increase ECM1 protein levels in the breast cancer cells

ECM1 protein levels in HCC1806 cells after receiving ECM1-construct-loaded sEVs treatments. Shown is mean ± SD; n = 3 individual experiments; two-sided unpaired *t*-test; p values are indicated in graphs. C-sEVs, circulating sEVs in CD-fed C57BL/6 mice; ECM-sEVs, ECM1 construct-loaded C-sEVs; ECM1, extracellular matrix protein 1. Source data are provided as a Source Data file.