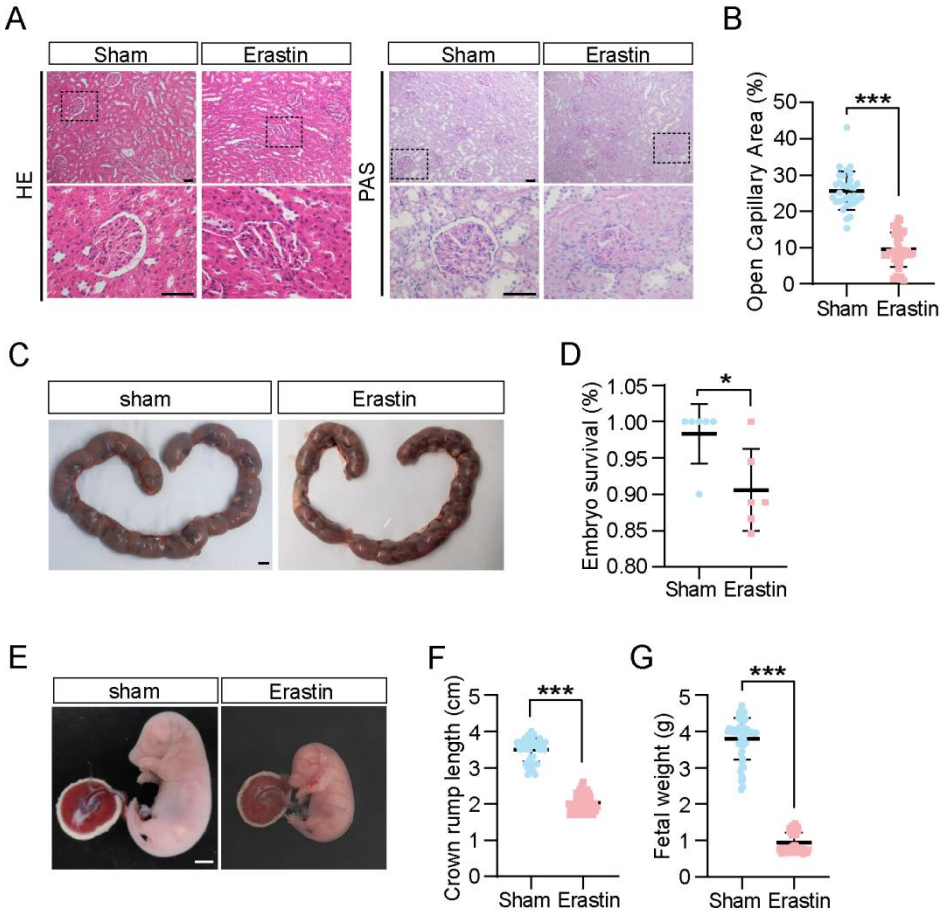
Contents

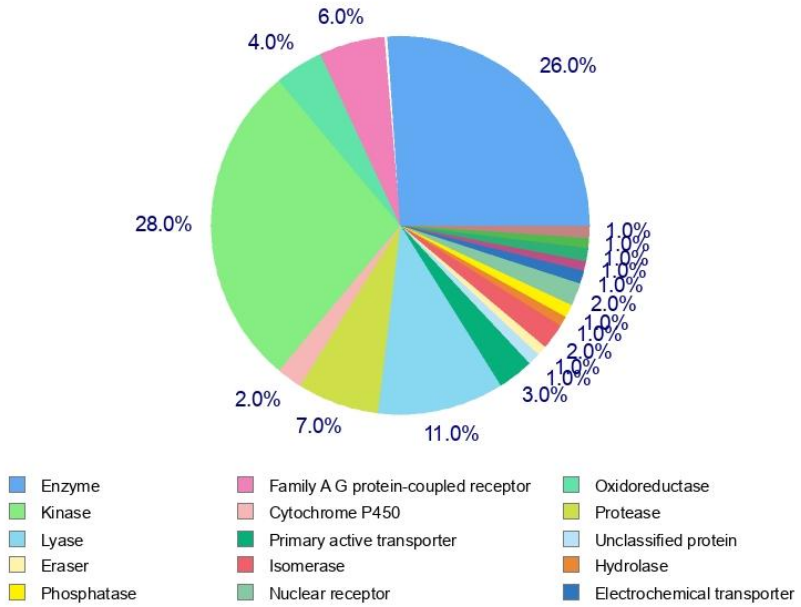
Supplementary Figures

Supplementary Figure 1



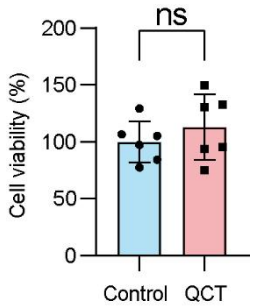
Supplementary Figure 1. Assessing pregnant rat model of ferroptosis by intraperitoneally injection of Erastin. **(A-B)** Representative images of glomeruli stained with HE and PAS (A) and the open capillary areas from the Sham and Erastin groups (B) (n = 32 in Sham, n = 39 in Erastin). **(C-D)** Gross images (C) and statistical map of embryonic survival (D) (n = 6 per group). **(E-G)** Gross photograph (E) of fetus and statistical diagrams of crown rump length (F) and fetal weight (G) (n = 51 in Sham, n = 89 in Erastin). Scale bars = 100 μm in (A), = 0.5 cm in (C) and (E). The error bars in figure represent median and 25–75% quartiles. *P < 0.05; ***P < 0.001.

Supplementary Figure 2



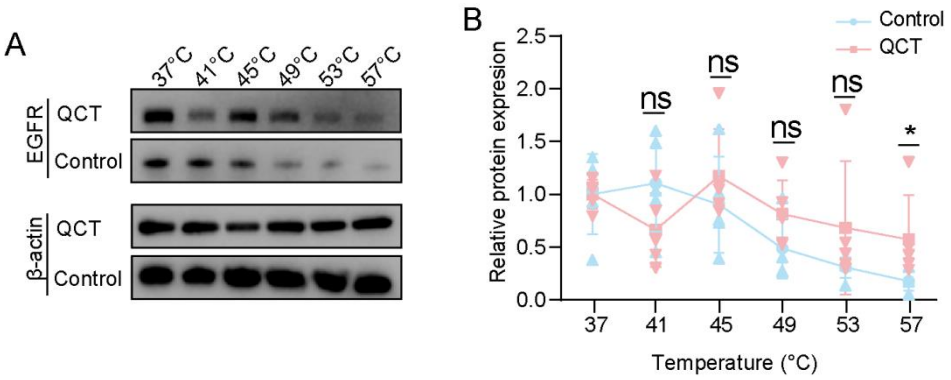
Supplementary Figure 2. Classification of predicted targets of QCT. The categorization of predicted targets and their proportion statistical chart.

Supplementary Figure 3



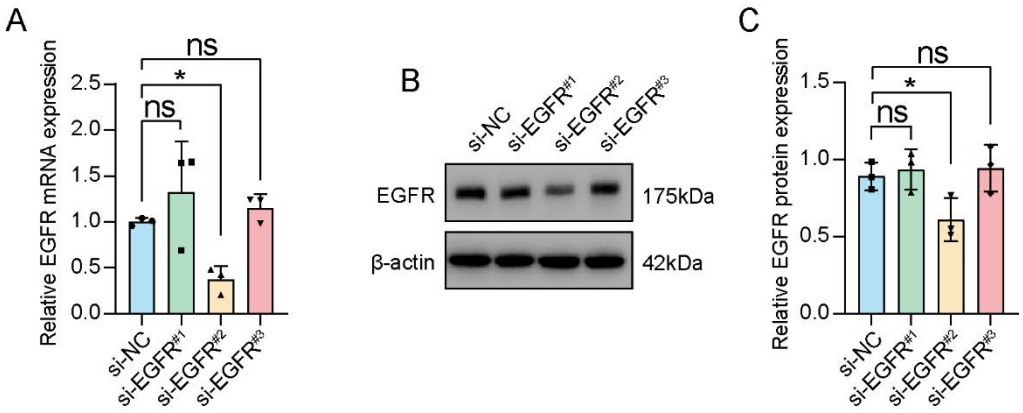
Supplementary Figure 3. Assessment of the effect of 60 μM QCT on cell viability. CCK-8 showing the effect of QCT on cell viability (n = 6 per group). The error bars in figure represent means ± SD. ns = no significance.

Supplementary Figure 4



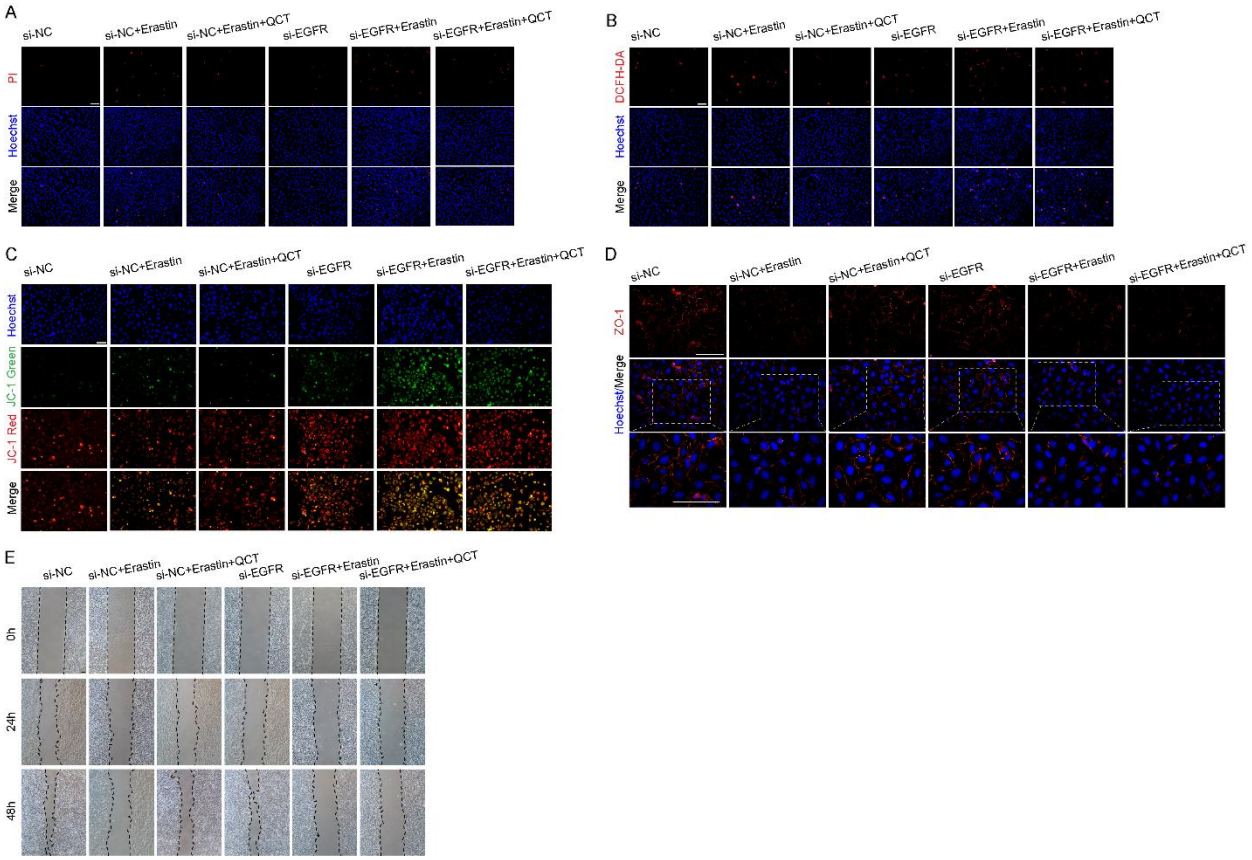
Supplementary Figure 4. The cellular thermal shift assay at low concentration of QCT (1 μM). **(A-B)** Representative Western blot images of cellular thermal shift assay (A) and the line graph of quantitative analysis of relative expressions of EGFR from the Control and QCT groups (B) (n = 5 per group of each temperature). The error bars in figure represent means ± SD. ns = no significance; *P < 0.05.

Supplementary Figure 5



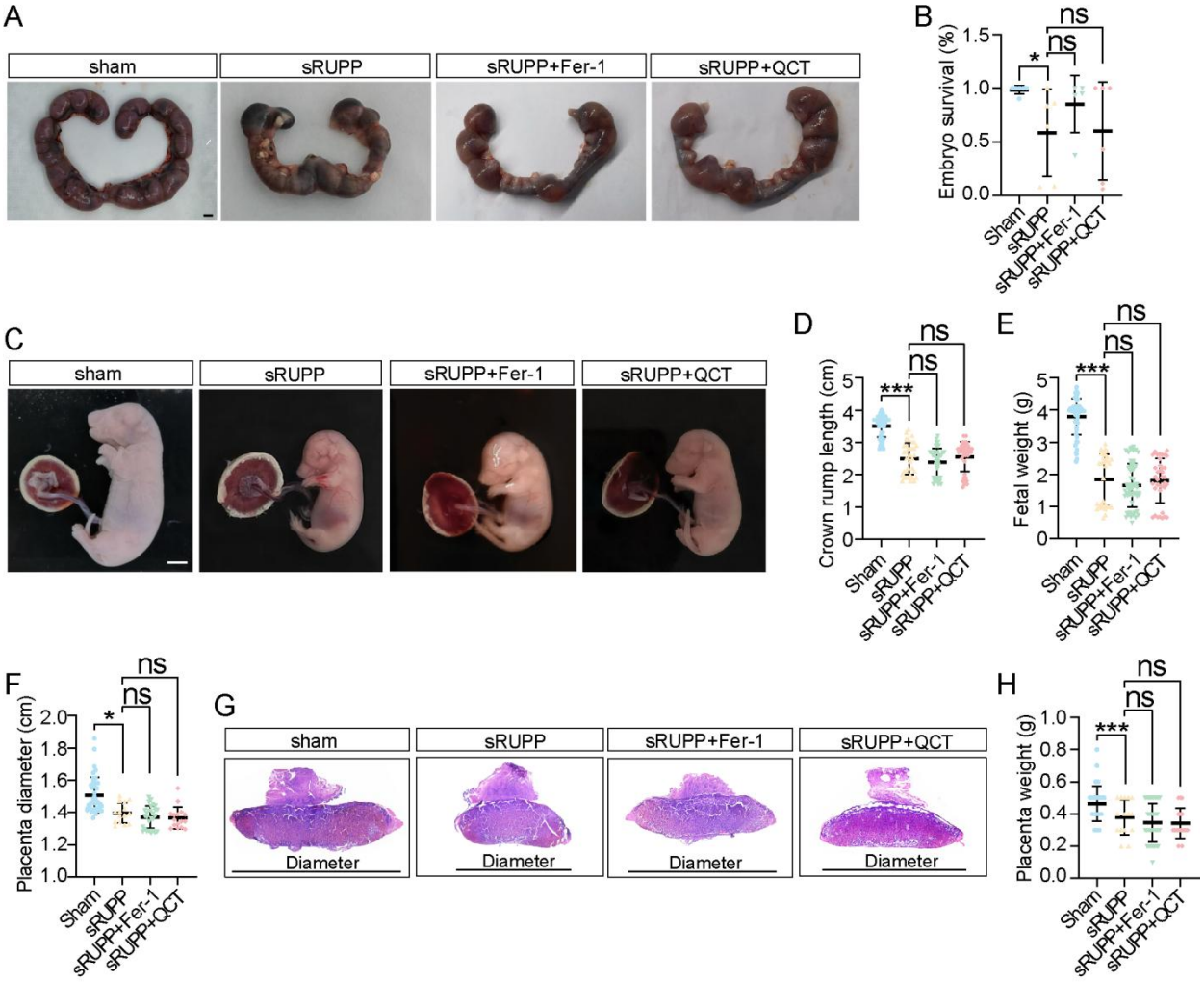
Supplementary Figure 5. Validation of si-EGFR effective chain. **(A)** The relative mRNA expression of EGFR from the si-NC, si-EGFR$^{\#1}$, si-EGFR$^{\#2}$ and si-EGFR$^{\#3}$ groups (n = 3 per group). **(B-C)** Representative Western blot images (B) and bar charts of quantitative analysis of relative expressions of EGFR (C) from the aforementioned four groups (n = 3 per group). The error bars in figure represent means ± SD. ns = no significance; *P < 0.05.

Supplementary Figure 6



Supplementary Figure 6. Assessing the cell death, cellular ROS, mitochondrial membrane potential change and endothelial function after down-regulation of EGFR. (A) Representative fluorescent detection of PI from the si-NC, si-NC+Erastin, si-NC+Erastin+QCT, si-EGFR, siEGFR+Erastin and si-EGFR+Erastin+QCT groups. **(B)** Representative fluorescent detection of DCFH-DA from the aforementioned six groups. **(C)** Representative fluorescent detection of JC-1 from the aforementioned six groups. **(D)** Representative images of ZO-1 immunofluorescence staining of HUVEC from the aforementioned six groups. **(E)** Representative images of scratch experiment of HUVEC from the aforementioned six groups. Scale bars = 100 μm in figure.

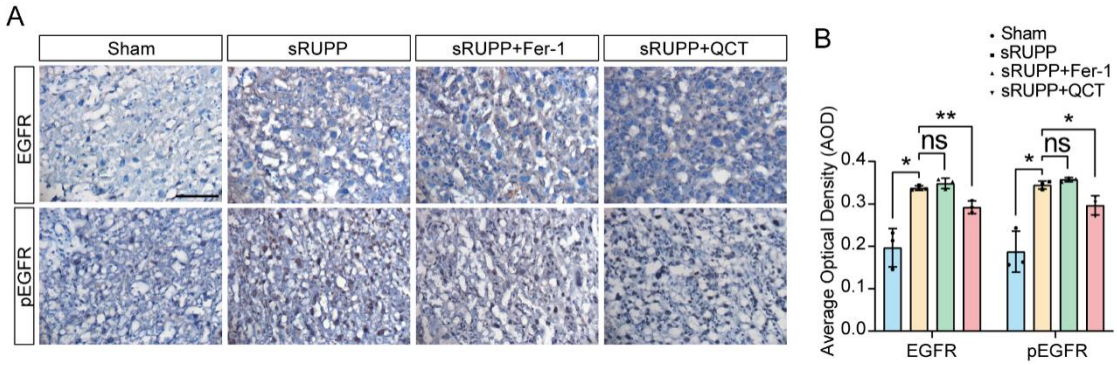
Supplementary Figure 7



Supplementary Figure 7. Analysis of the PE indicators in rat model of sRUPP, sRUPP+Fer-1 and sRUPP+QCT. **(A-B)** Gross images (A) and statistical map of embryonic survival (B) (n = 6 in Sham, n = 6 in sRUPP, n = 5 in sRUPP+Fer-1, n = 6 in sRUPP+QCT). **(C-E)** Gross photograph (C) of fetus and statistical diagrams of crown rump length (D) (n = 51 in Sham, n = 37 in sRUPP, n = 43 in sRUPP+Fer-1, n = 38 in sRUPP+QCT) and fetal weight (E) (n = 51 in Sham, n = 32 in sRUPP, n = 57 in sRUPP+Fer-1, n = 37 in sRUPP+QCT). **(F-H)** Placental diameter (F) (n = 40 in Sham, n = 15 in sRUPP, n = 36 in sRUPP+Fer-1, n = 17 in sRUPP+QCT), HE staining of placental sections (G) and placental weight (H) (n = 40 in Sham, n = 15 in sRUPP, n = 28 in sRUPP+Fer-1, n = 16 in sRUPP+QCT). Scale bars = 0.5 cm in (A)

and (C). The error bars in figure represent median and 25–75% quartiles. ns = no significance; *P < 0.05; ***P < 0.001.

Supplementary Figure 8



Supplementary Figure 8. Expression of EGFR and pEGFR in labyrinth zone of placenta of Sham, sRUPP, sRUPP+Fer-1 and sRUPP+QCT. (A-B) Representative images of immunohistochemical staining of EGFR and pEGFR from the labyrinth zone of Sham, sRUPP, sRUPP+Fer-1 and sRUPP+QCT groups (A), and the bar charts of average optical density (AOD) (B) (n = 3 per group). Scale bars = 100 μm in figure. The error bars in figure represent means ± SD. ns = no significance; *P < 0.05; **P < 0.01.

Supplementary Tables

Supplementary Table 1. Inclusion and exclusion criteria.

Overall Inclusion criteria
■ Chinese
■ Obtain patient informed consent
■ Meeting the diagnostic criteria for preeclampsia
■ Age: 18–45 years
■ Singleton pregnancy
■ Free of chronic diseases (kidney disease diabetes, hypertension, or other chronic diseases), autoimmune disorders, infections, or hepatitis in preconception
Overall Exclusion criteria
◆ Not obtaining patient informed consent
◆ Infectious or autoimmune diseases or complicated with serious internal or surgery-related disease
◆ Gestational diabetes or other pregnancy complications or chronic comorbidities
◆ Chronic hypertension
◆ Multi-fetal gestation

Supplementary Table 2. Clinical and laboratory characteristics of the study population.

Variables	Control	PE	*P* value
The analysis of plasma			
Sample size	n = 72	n = 72	
Maternal age (years)	30 (27 – 34)	36 (35 – 38)	< 0.001
Prepregnancy BMI (kg/m^2)	20 (19 – 22)	24 (21 – 26)	< 0.001
Gestational age at birth (days)	261 (255 – 275)	255.50 (229 – 265.50)	< 0.001
FGR, n (%)	2 (2.78)	29 (40.28)	< 0.001
Family history of PE, n (%)	1 (1.39)	14 (19.44)	< 0.001
MAP (mmHg)	75 (70.25 – 80)	123 (114 – 132)	< 0.001
24-hour proteinuria (g/24h)	/	2.21 (1.14 – 4.25)	
Fetal birth weight (g)	3227.5 (3126.50 – 3368)	2560 (1606.50 – 3197.25)	< 0.001
ARDS, n (%)	0 (0)	21 (29.17)	< 0.001
NICU, n (%)	0 (0)	21 (29.17)	< 0.001
The analysis of placenta			
Sample size	n = 34	n = 34	
Maternal age (years)	31 (28.75 – 35)	36.50 (35 – 39)	< 0.001
Prepregnancy BMI (kg/m^2)	20 (18.75 – 21.25)	24.50 (21 – 27.25)	< 0.001
Gestational age at birth (days)	273.50 (266.50 – 280.25)	239.50 (212 – 261)	< 0.001
FGR, n (%)	1 (2.94)	21 (61.76)	< 0.001
Family history of PE, n (%)	0 (0)	3 (8.82)	0.239
MAP (mmHg)	75.50 (71.50 – 79.25)	130 (118 – 134)	< 0.001
24-hour proteinuria (g/24h)	/	3.07 (1.46 – 5.17)	
Fetal birth weight (g)	3241 (3125.50 – 3370.50)	1825 (1475 – 2650)	< 0.001
ARDS, n (%)	0 (0)	16 (47.06)	< 0.001
NICU, n (%)	0(0)	15 (44.12)	< 0.001

Supplementary Table 3. Sequences of si-RNA.

si-RNA	Sequence
si-NC-F	5’-UUCUCCGAACGUGUCACGUTT-3’
si-NC-R	5’-ACGUGACACGUUCGGAGAATT-3’
si-EGFR$^{\#1}$-F	5’-CGCAAAGUGUGUAACGGAAUATT-3’
si-EGFR$^{\#1}$-R	5’-UAUUCCGUUACACACUUUGCGTT-3’
si-EGFR$^{\#2}$-F	5’-CAGCAUGUCAAGAUCACAGAUTT-3’
si-EGFR$^{\#2}$-R	5’-AUCUGUGAUCUUGACAUGCUGTT-3’
si-EGFR$^{\#3}$-F	5’-GCCACAAAGCAGUGAAUUUAUTT-3’
si-EGFR$^{\#3}$-R	5’-AUAAAUUCACUGCUUUGUGGCTT-3’

Supplementary Table 4. Antibodies for Histological analysis.

Antibody	Concentration	Article Number	Company	Country
ZO-1	1:1000	21773-1-AP	Proteintech	USA
Caveolin 1	1:400	PA5-17447	Thermo Fisher Scientific	USA
EGFR	1:100	bsm-52317R	Bioss	China
pEGFR (Tyr1068)	1:100	bsm-52149R	Bioss	China

Supplementary Table 5. Antibodies for Western blot.

Antibody	Concentration	Article Number	Company	Country
GPX4	1:3000	ab125066	Abcam	USA
ACSL4	1:2000	ab155282	Abcam	USA
SLC7A11	1:3000	ab175186	Abcam	USA
EGFR	1:1000	4267S	Cell Signaling Technology	USA
pEGFR (Tyr1068)	1:1000	bsm-52149R	Bioss	China
AKT1/2/3	1:1000	T55561	Abmart	China
pAKT (Ser473)	1:1000	T40067	Abmart	China
ERK1/2	1:1000	T40071	Abmart	China
pERK1(T202/Y204) + ERK2(T185/Y187)	1:1000	T40072	Abmart	China
β-actin	1:10000	60008-1-1g	Proteintech	USA

Supplementary Table 6. ELISA kits and related kits for oxidative stress detection.

Name	Article Number	Company	Country
MDA	MB-3866B	SMB	China
GSH	MB- 0458B	SMB	China
GSH-Px	MB-3866B	SMB	China
Fe^{2+}	E-BC-K773-M-96T(80samples)	Elabscience	China
IL-6 (human)	MB-0049A	Mbbiology Biological	China
IL-10 (human)	MB-3705A	Mbbiology Biological	China
TNF-α (human)	MB-0122A	Mbbiology Biological	China
sFlt-1 (human)	MB-4521A	Mbbiology Biological	China
PLGF (human)	MB-0099A	Mbbiology Biological	China
IL-6 (rat)	MB-1731A	Mbbiology Biological	China
IL-10 (rat)	MB-1736A	Mbbiology Biological	China
TNF-α (rat)	MB-1721A	Mbbiology Biological	China
sFlt-1 (rat)	MB-6627A	Mbbiology Biological	China
UP (rat)	MB-6875A	Mbbiology Biological	China
DCFH-DA (Green)	D6470	Solarbio	China
DCFH-DA (Red)	GC30025-10mg	GLPBIO	USA
PI	DH260-1	Sigma-Aldrich	USA
JC-1	GK3610	Genview	USA

Supplementary Table 7. Predicted targets of QCT.

Target	Probability	Target	Probability	Target	Probability	Target	Probability
NOX4	1	**SRC**	**1**	ALK	1	PIK3CG	0.68
AVPR2	1	PTK2	1	**AKT1**	**1**	APEX1	0.68
AKR1B1	1	HSD17B2	1	ABCB1	1	PTPRS	0.55
XDH	1	KDR	1	NEK6	1	ESR2	0.55
MAOA	1	MMP13	1	PLA2G1B	1	MPG	0.55
IGF1R	1	MMP3	1	CA5A	1	SLC22A12	0.55
FLT3	1	CA3	1	BACE1	1	CDK5R1 CDK5	0.54
CYP19A1	1	ALOX15	1	CYP1B1	1	CCNB3 CDK1 CCNB1 CCNB2	0.54
EGFR	**1**	ABCC1	1	AXL	1	ARG1	0.54
F2	1	PLK1	1	ABCG2	1	CDK6	0.50
CA2	1	CA6	1	NUAK1	1	CDK2	0.50
PIM1	1	CDK1	1	AKR1C2	1	TYR	0.40
ALOX5	1	MMP9	1	AKR1C1	1	HSD17B1	0.40
AURKB	1	CA12	1	AKR1C3	1	AHR	0.40
DRD4	1	MMP2	1	AKR1C4	1	ESRRA	0.40
ADORA1	1	PKN1	1	CA13	1	APP	0.26
CA7	1	CA14	1	AKR1A1	1	PARP1	0.26
GLO1	1	CA9	1	GPR35	1	TTR	0.26
MPO	1	CSNK2A1	1	MAPT	0.68	MMP12	0.26
PIK3R1	1	ALOX12	1	KDM4E	0.68	CD38	0.26
ADORA2A	1	MET	1	TOP2A	0.68	AKR1B10	0.26
DAPK1	1	CA4	1	INSR	0.68	TNKS2	0.26
PYGL	1	NEK2	1	ACHE	0.68	TNKS	0.26
CA1	1	CXCR1	1	MYLK	0.68	TOP1	0.26
GSK3B	1	CAMK2B	1	SYK	0.68	TERT	0.20

Supplementary Table 8. Primers for qPCR.

Primer	sequence
IL-6-F	5’-AGACAGCCACTCACCTCTTCAG-3’
IL-6-R	5’-TTCTGCCAGTGCCTCTTTGCTG-3’
IL-10-F	5’-TCTCCGAGATGCCTTCAGCAGA-3’
IL-10-R	5’-TCAGACAAGGCTTGGCAACCCA-3’
TNF-α-F	5’-CTCTTCTGCCTGCTGCACTTTG-3’
TNF-α-R	5’-ATGGGCTACAGGCTTGTCACTC-3’
EGFR-F	5’-AACACCCTGGTCTGGAAGTACG-3’
EGFR-R	5’-TCGTTGGACAGCCTTCAAGACC-3’
GAPDH-F	5’-GTCTCCTCTGACTTCAACAGCG-3’
GAPDH-R	5’-ACCACCCTGTTGCTGTAGCCAA-3’

Western Blot Images

Figure 1B

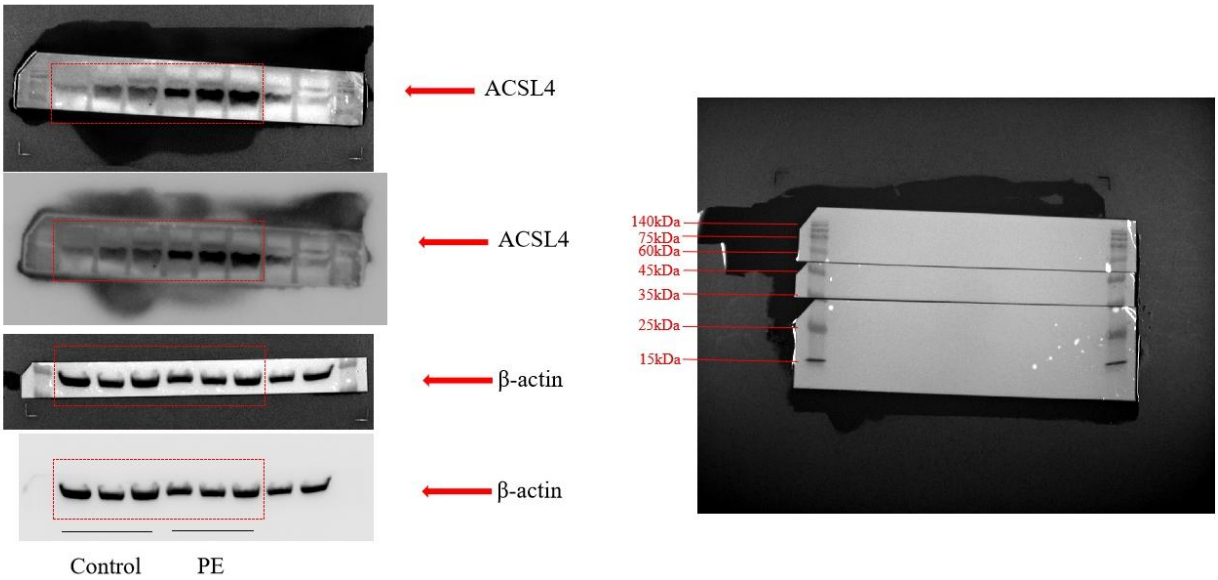


Figure 1B

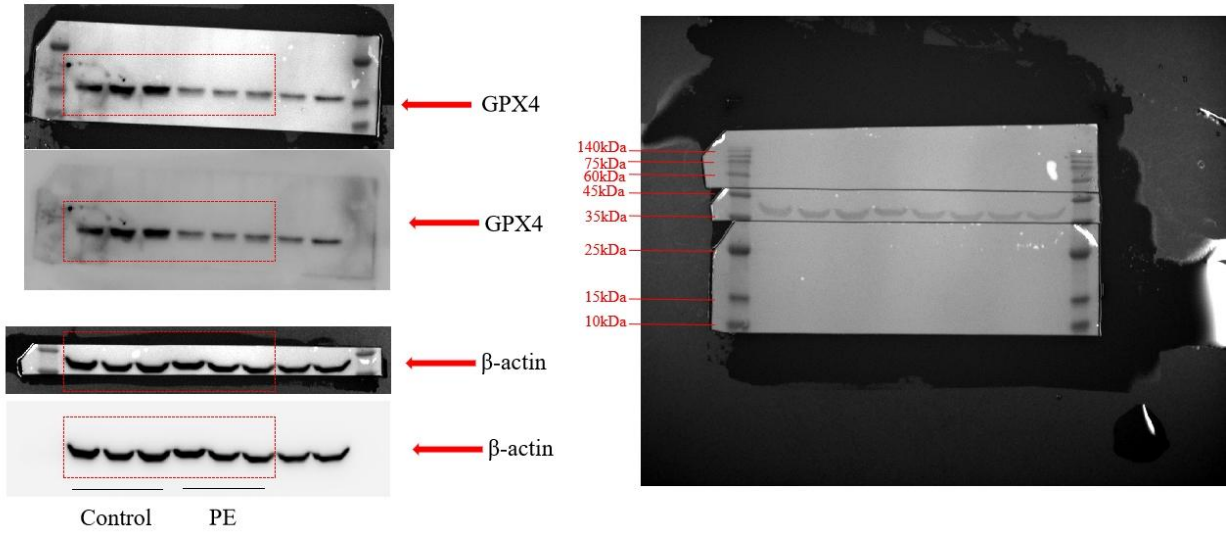


Figure 1B

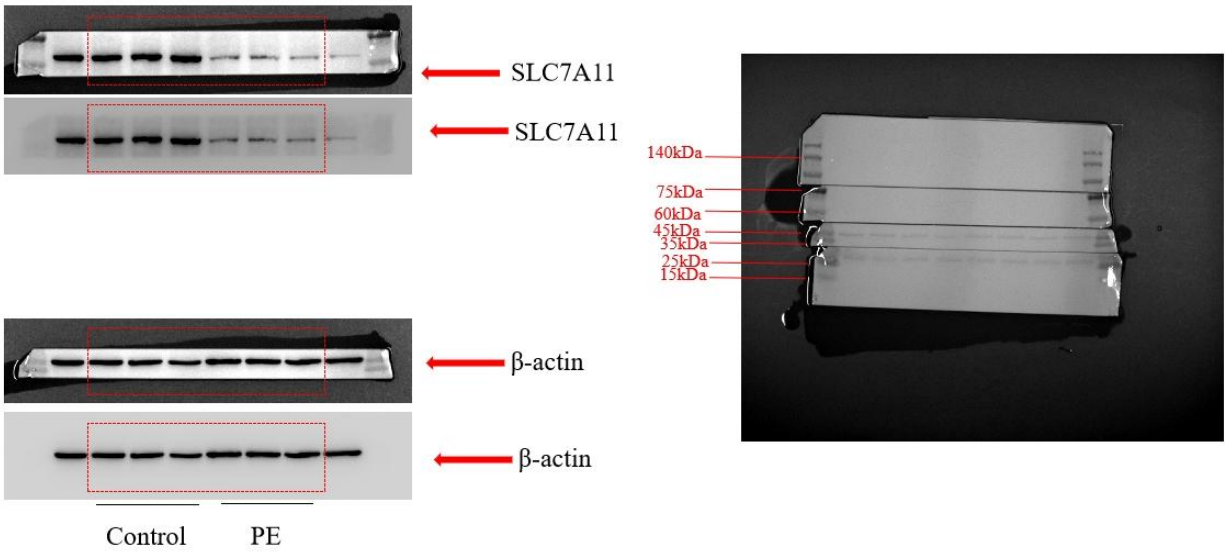


Figure 2G

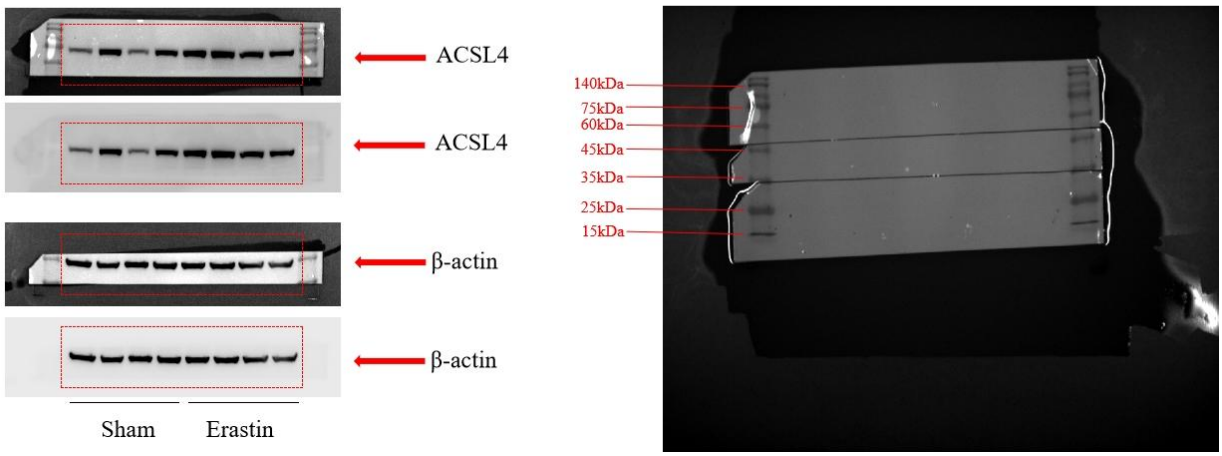
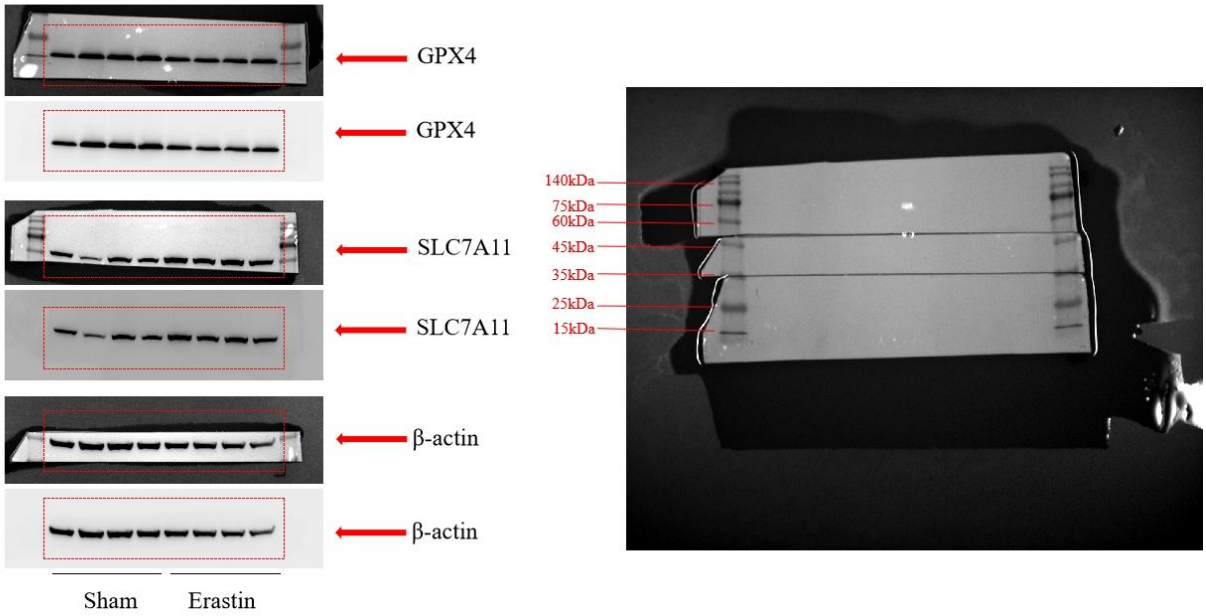


Figure 2G



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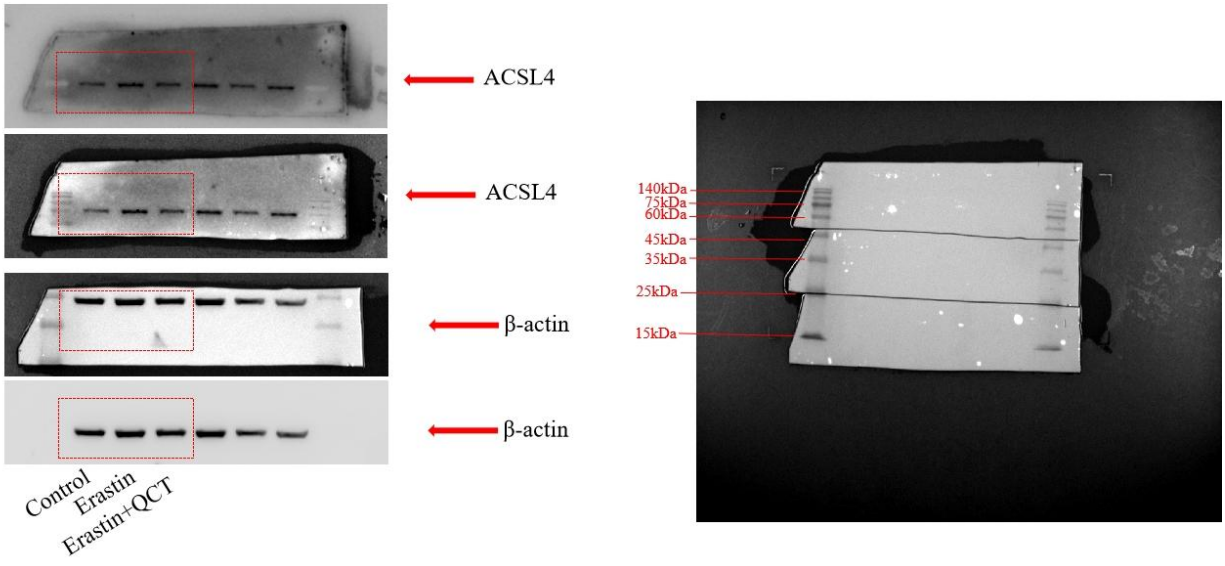
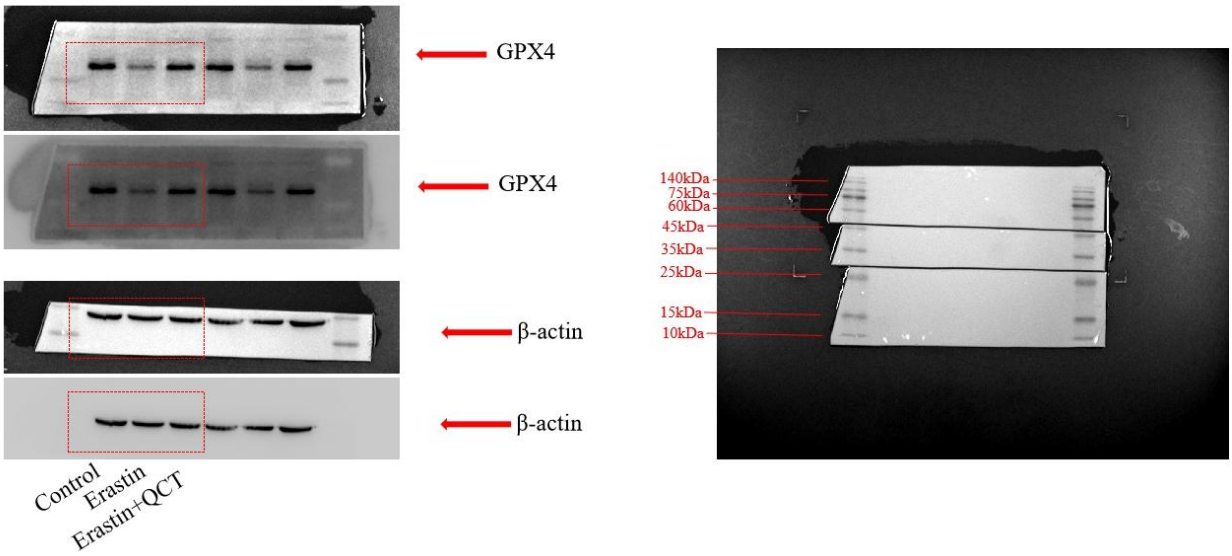


Figure 3G



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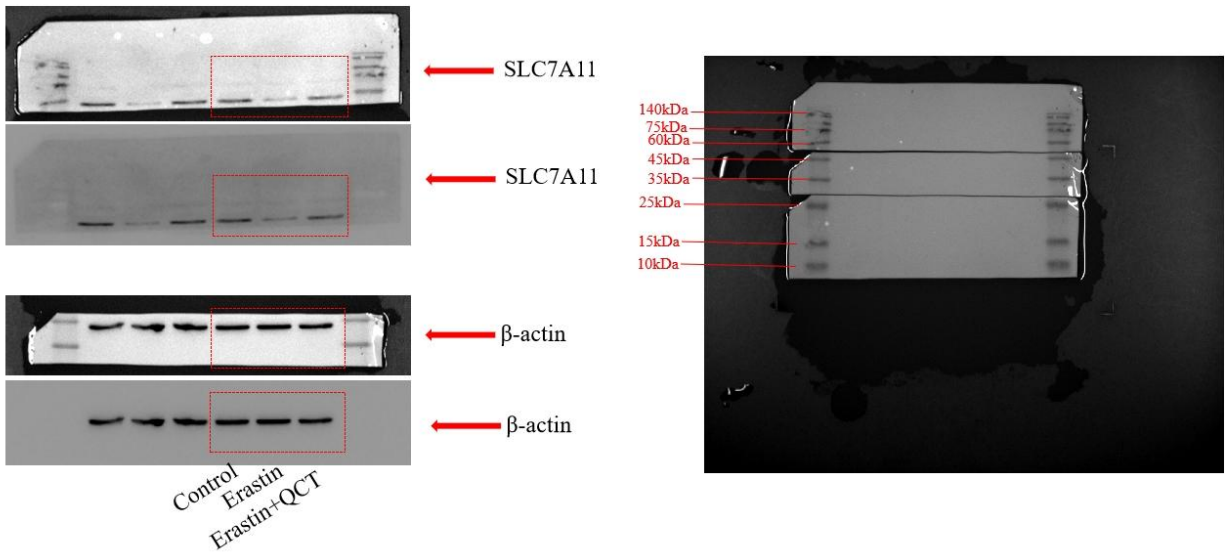
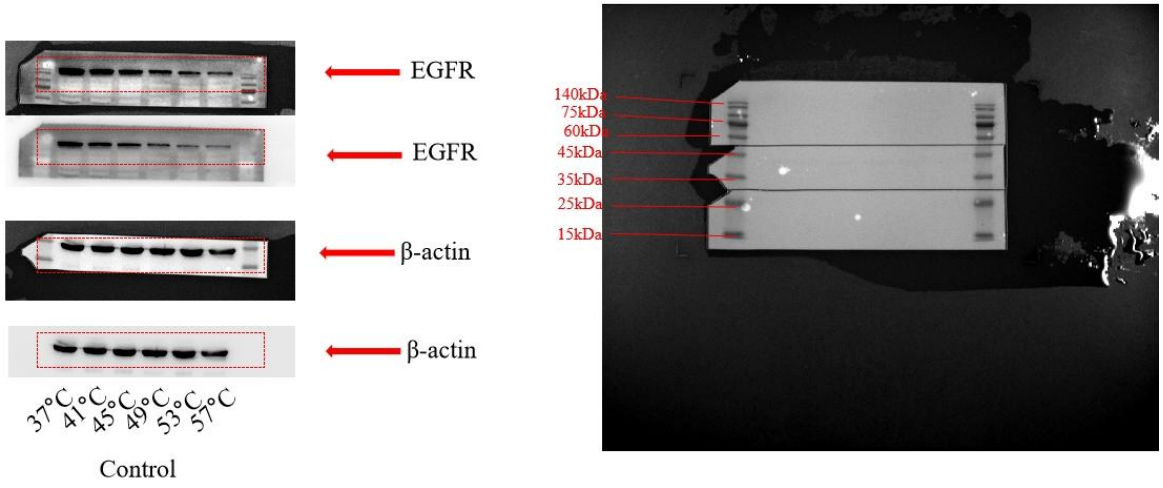


Figure 5G



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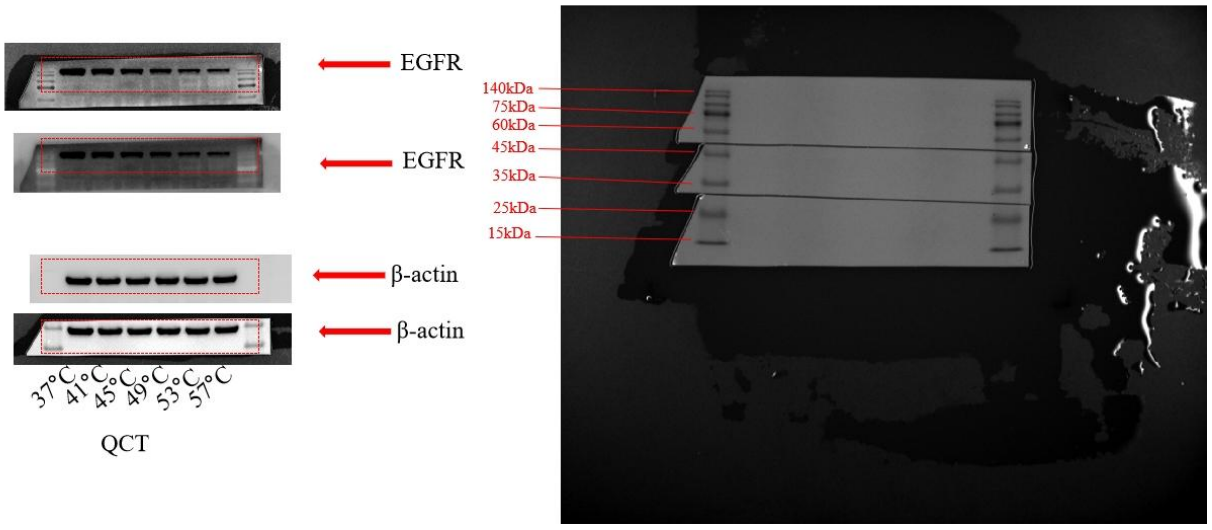

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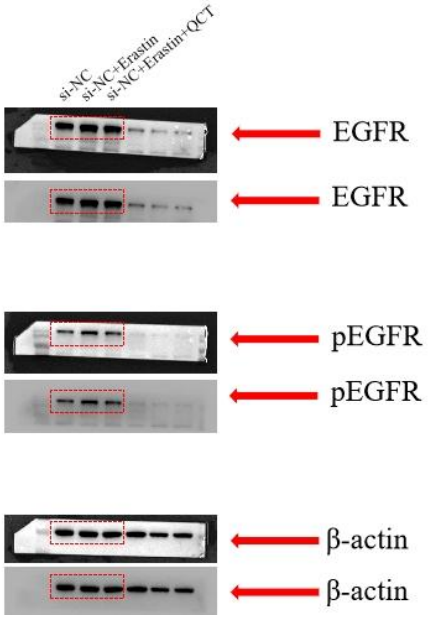


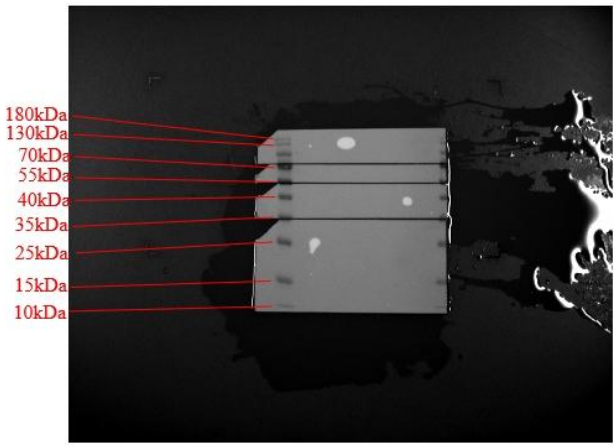
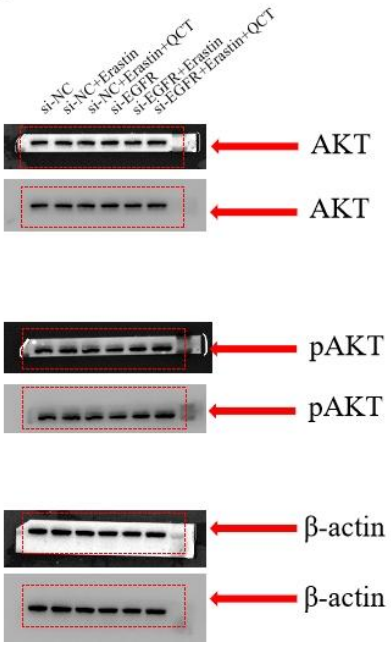


Figure 6G



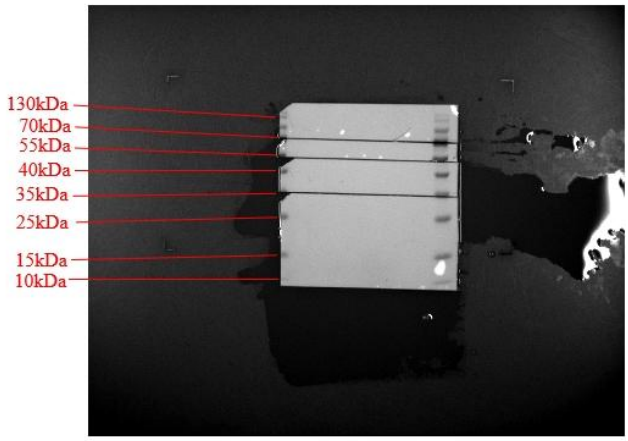
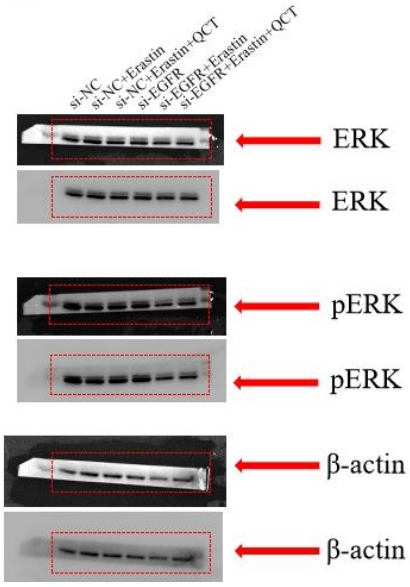


Figure 6G



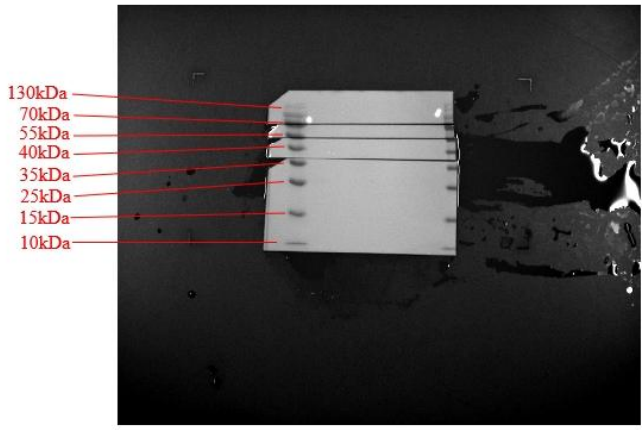


Figure 6G

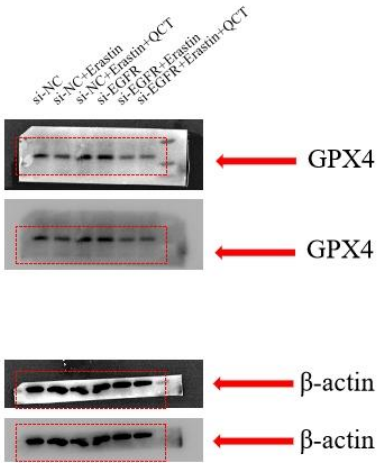


Figure 8A

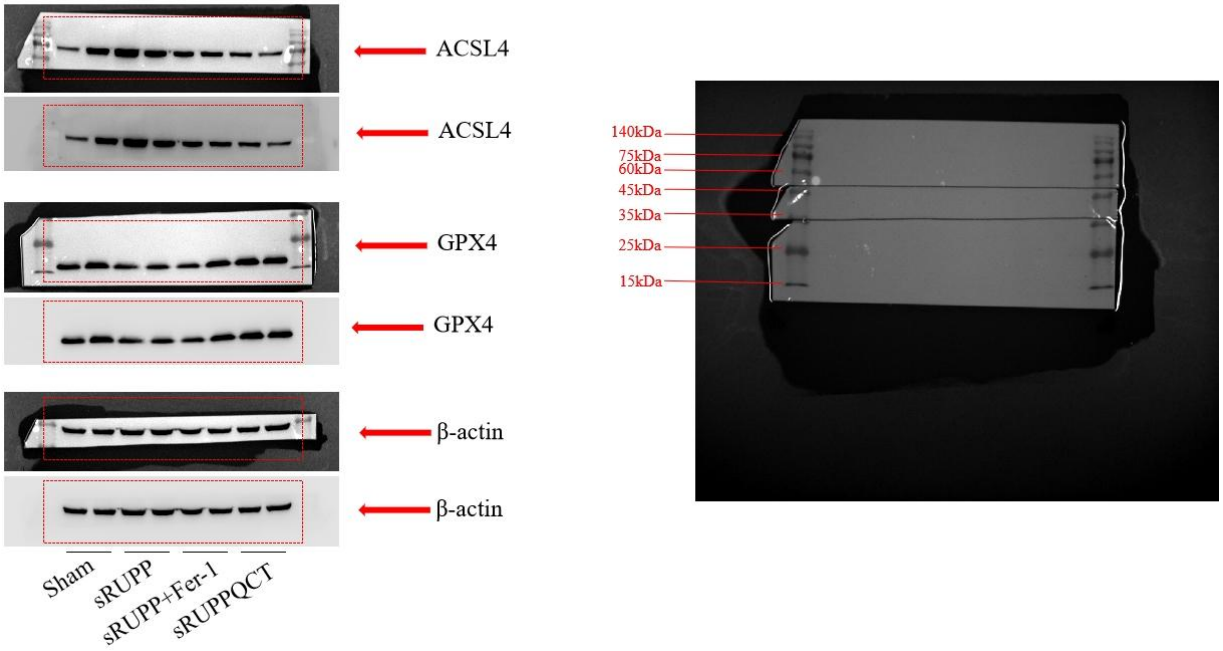
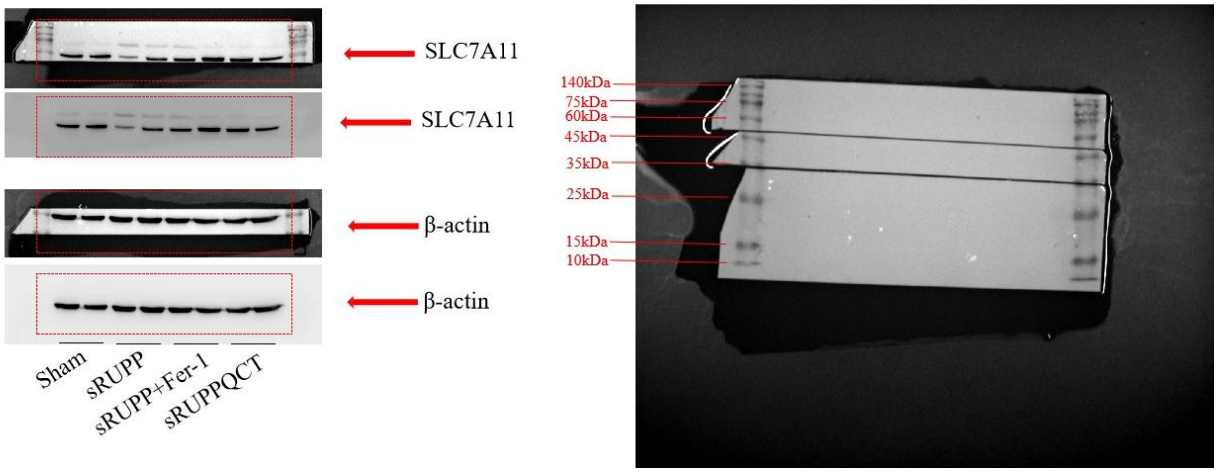
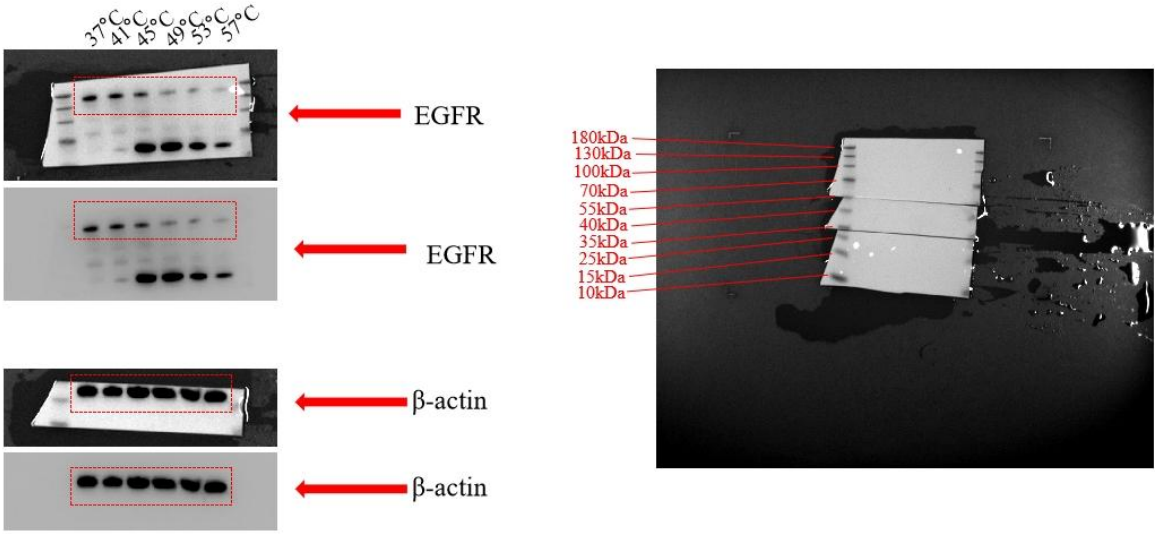


Figure 8A

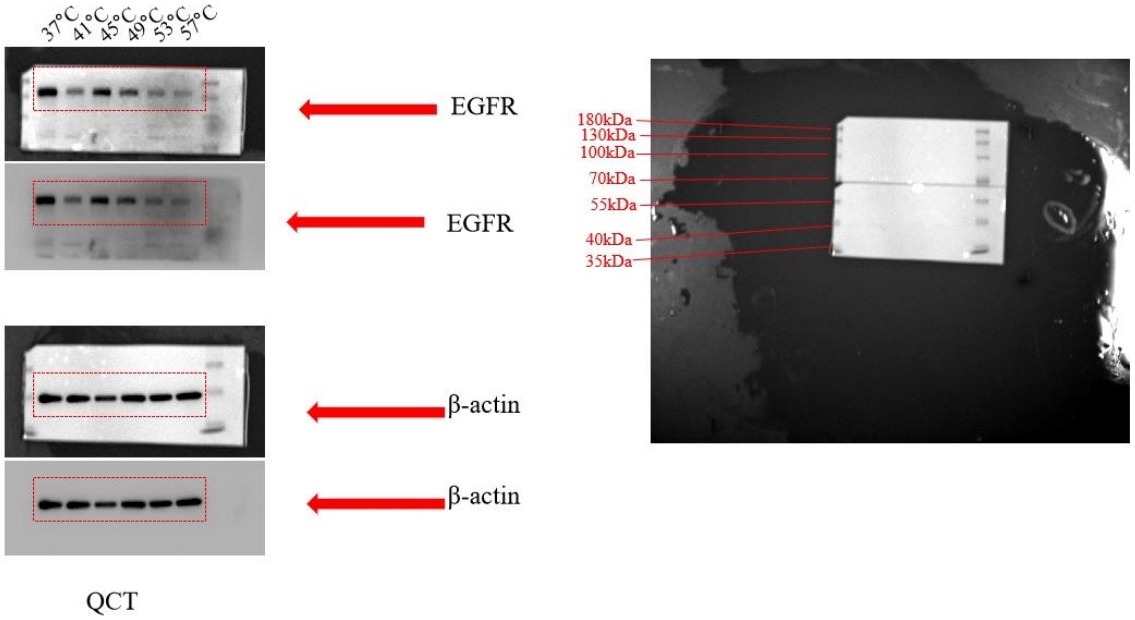


Supplementary Figure 4A



Control

Supplementary Figure 4A



QCT

Supplementary Figure 5B