Supporting information

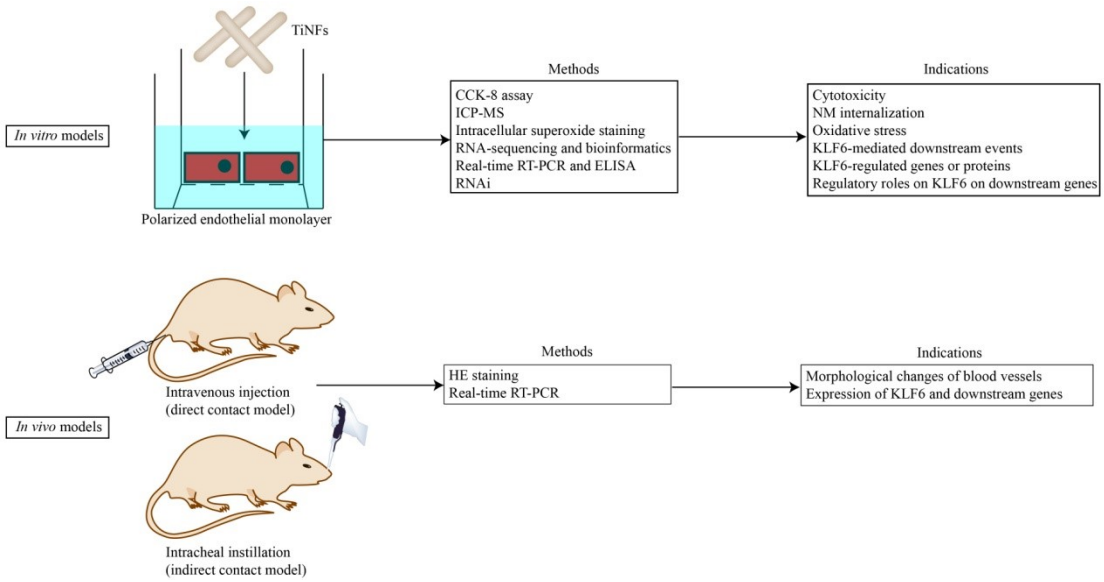

Figure S1. The schematic illustration of study design. This study used both *in vitro* models and *in vivo* models. The *in vitro* models were based on long-term cultivated HUVECs on cell culture inserts. The *in vivo* models were based on C57BL/6 mice, which were intravenously injected (direct contact model) or intratracheally instilled with TiNFs (indirect contact model). The experiments carried out on each model and the indications for each experiment were indicated in Figure S1. For more information, see the main text.

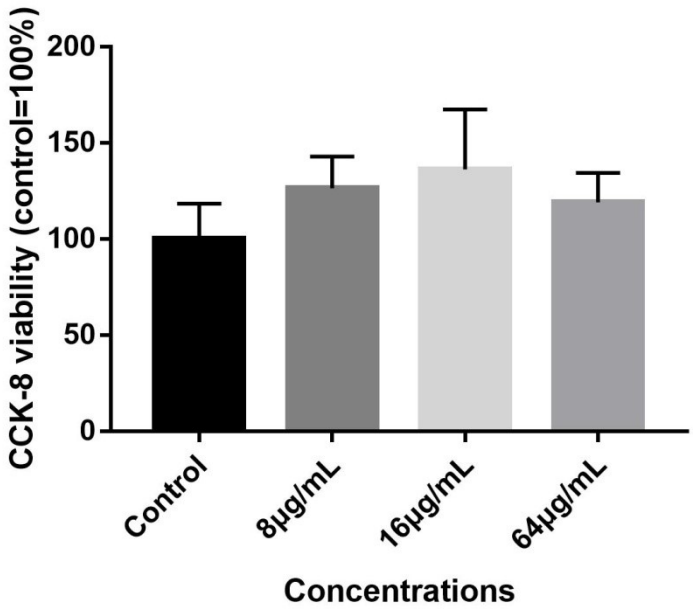

Figure S2. The changes of cellular viability. HUVECs grown in cell culture inserts were exposed to various concentrations of TiNFs for 24 h, and then the cellular viability was measured by CCK-8 assay.

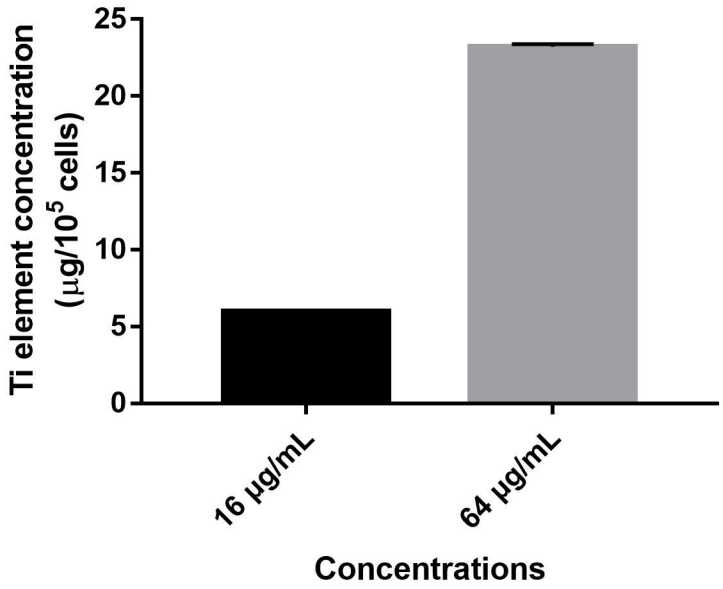

Figure S3. The increase of intracellular Ti element concentration. HUVECs grown in cell culture inserts were exposed to 16 or 64 μg/mL TiNFs for 24 h, and Ti elemental concentrations were measured by ICP-MS.

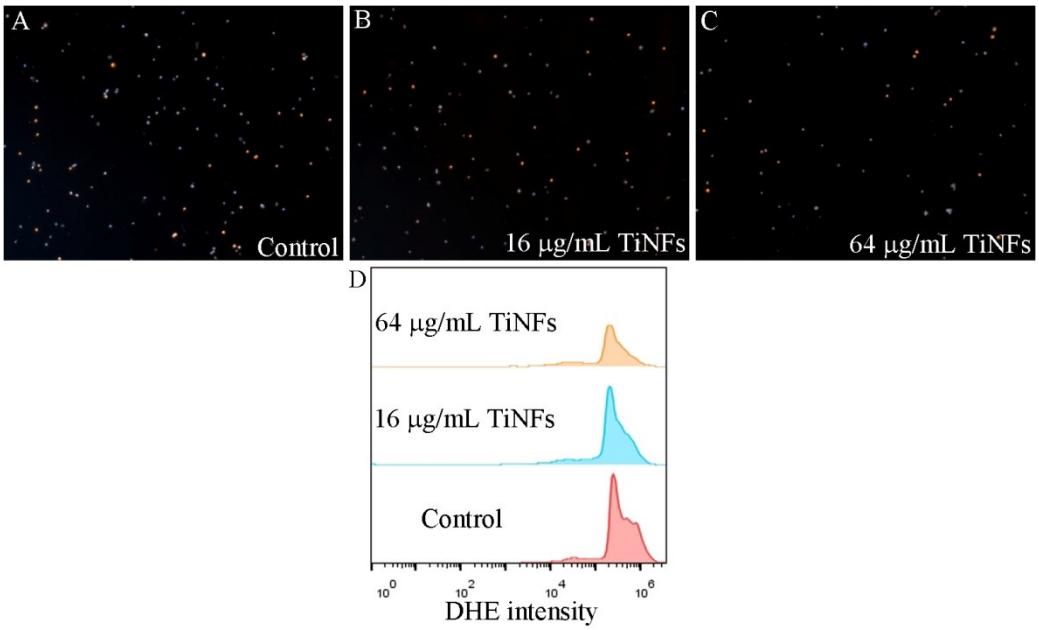

Figure S4. The changes of intracellular superoxide. HUVECs grown in cell culture inserts were incubated with 0 (S4A), 16 (S4B) or 64 μg/mL (S4C) TiNFs for 24 h. After the exposure, the cells were removed from cell culture inserts by using trypsin and counterstained by DHE (orange fluorescence, to stain superoxide) and Hoechst 33342 (blue fluorescence, to stain nuclei). The changes of DHE intensity were shown in Figure S4D.

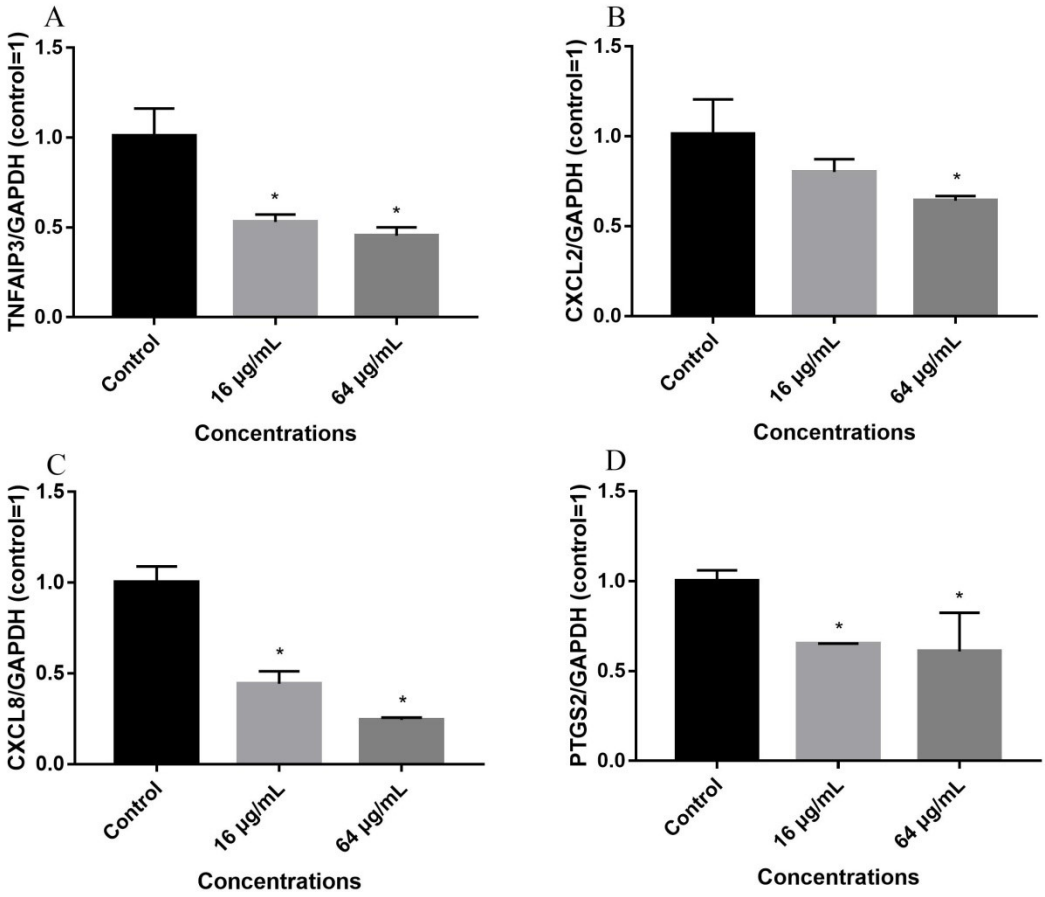

Figure S5. The mRNA levels of TNFAIP3 (S5A), CXCL2 (S5B), CXCL8 (S5C) and PTGS2 (S5D). HUVECs grown in cell culture inserts were exposed to various concentrations of TiNFs for 24 h, and the expression of KLF-related genes was measured by real-time RT-PCR. *, $p<0.05$, compared with control.

Table S1. The forward and reverse primers used for real-time RT-PCR (for *in vitro* studies).

Gene names	Forward primers	Reverse primers
GAPDH	ACAGCCTCAAGATCATCAGC	GGTCATGAGTCCTTCCACGAT
ATF3	AAAACCAGGATGCCCACCGTT	CCACATCCCCTACGAGTGACA
KLF6	CCCACGGCCAAGTTTACCTC	AAGGCTTTTCTCCTGGCTTCC
CCL2	CCTAGCTTTCCCCAGACACC	AAAAGCAATTTCCCCAAGTCTC
TNFAIP3	TCCTCAGGCTTTGTATTTGAGC	TGTGTATCGGTGCATGGTTTTA
CXCL2	GTCTCAACCCCGCATCG	TCAGTTGGATTTGCCATTTT
CXCL8	CCAAGGGCCAAGAGAATATCCGAA	AAATAAAGGAGAAACCAAGGCACA
PTGS2	CTCTATCACTGGCATCCCCTT	CATTCCTACCACCAGCAACCC

Table S2. The forward and reverse primers used for real-time RT-PCR (for *in vivo* studies).

Gene names	Forward primers	Reverse primers
gapdh	CGACTTCAACAGCAACTCCCACTCTTCC	TGGGTGGTCCAGGGTTTCTTACTCCTT
klf6	CTGCAGGAAAGTTTACACGAAA	GTCAACTCATCACTTCTTGCAA
atf3	GAGGATTTTGCTAACCTGACACC	GAGGATTTTGCTAACCTGACACC
ccl2	TTTTTGTCACCAAGCTCAAGAG	TTCTGATCTCATTTGGTTCCGA

Table S3. The KLF6 siRNA sequences used in this study.

	Sense (5'-3')	Antisense (5'-3')
KLF6 siRNA-287	GmsUmsUmAmCfAmAfCfUfUmAmGmAmGmAmCmCmAmAm	UmsUfsGmGmUmCfUmCfUfAmAmGmUmUfGmUfAmAmCmsAmsAm
KLF6 siRNA-621	CmsAmsGmGmAfAmAfGfUfUmUmAmCmAmCmCmAmAmAm	UmsUfsUmGmGmUfGmUfAfAmAmCmUmUfUmCfCmUmGmsCmsAm

Note: The modifications: m means the modifications with methoxy groups at 2', f means the modifications with F groups at 2'; and s means thiophosphate groups between the bases.

Table S4. The complete list of KLF6-related genes. HUVECs grown in cell culture inserts were exposed to 64 μg/mL TiNFs for 24 h before analysis. Data were average FPKM values ± SD of triplicate.

Gene name	Control	TiNFs	Regulation	log2(fc)	P value	Significant
CCL2	5.40±0.38	29.88±0.40	up	2.47	0.00	yes
PTGS2	8.61±1.33	59.25±14.76	up	2.78	0.00	yes
CXCL2	1.08±0.12	8.04±0.94	up	2.89	0.00	yes
ATF3	0.26±0.14	2.93±0.44	up	3.51	0.00	yes
CXCL8	34.58±1.70	93.60±25.92	up	1.44	0.00	yes
TNFAIP3	0.94±0.03	3.32±0.61	up	1.82	0.00	yes
KLF4	0.55±0.22	2.32±0.44	up	2.07	0.00	yes
MKI67	21.03±2.71	10.69±2.80	down	-0.98	0.00	no
NFKB2	3.93±0.06	6.71±0.70	up	0.77	0.00	no
PLAU	10.72±0.47	16.85±0.36	up	0.65	0.00	no
NR2F1	14.00±0.39	8.61±0.99	down	-0.70	0.00	no
TNIP1	12.68±0.27	19.57±2.26	up	0.63	0.00	no
PCNA	59.84±3.96	38.65±3.73	down	-0.63	0.00	no
JUN	47.10±6.38	68.34±3.81	up	0.54	0.00	no

NFKBIA	10.38±0.57	15.56±1.45	up	0.58	0.00	no
POLA2	5.39±0.70	3.48±0.07	down	-0.63	0.00	no
PMAIP1	2.83±0.45	5.27±1.39	up	0.90	0.00	no
E2F1	4.14±0.78	2.23±0.39	down	-0.89	0.00	no
TGFBI	2.88±0.34	1.85±0.15	down	-0.64	0.00	no
BIRC5	4.11±1.02	2.55±0.24	down	-0.69	0.01	no
MNT	2.53±0.11	3.43±0.25	up	0.44	0.01	no
SDC1	4.78±0.72	3.16±0.41	down	-0.60	0.01	no
TFPI2	27.04±5.28	36.17±7.65	up	0.42	0.03	no
MAX	9.89±0.61	12.40±0.66	up	0.33	0.03	no
VEGFA	1.23±0.20	1.62±0.19	up	0.40	0.04	no
RELA	9.91±0.19	12.54±2.13	up	0.34	0.04	no
KLF6	14.76±12.21	29.96±20.21	up	1.02	0.05	no
IL6	2.00±0.22	2.96±0.70	up	0.57	0.05	no
CDK2	4.62±0.60	3.41±0.47	down	-0.44	0.06	no
MCL1	57.76±5.89	69.17±5.86	up	0.26	0.07	no
NR1D1	3.14±0.37	4.18±0.52	up	0.41	0.08	no
NSD1	6.48±1.05	7.65±0.12	up	0.24	0.11	no
NFKB1	8.63±0.07	10.12±0.33	up	0.23	0.11	no
BCL6	2.61±0.15	3.18±0.15	up	0.29	0.12	no
SP1	9.79±1.53	11.61±0.88	up	0.25	0.12	no
TAF9	16.61±0.93	13.67±1.30	down	-0.28	0.13	no
GSK3B	11.20±0.62	12.93±0.49	up	0.21	0.14	no
IGF1R	5.59±0.29	6.47±0.56	up	0.21	0.15	no
FBL	59.43±1.49	50.55±2.53	down	-0.23	0.15	no
NOP56	24.74±0.94	21.13±1.37	down	-0.23	0.17	no
CTNNB1	36.33±1.47	41.09±0.67	up	0.18	0.17	no
CREBBP	4.66±0.68	5.29±0.26	up	0.18	0.22	no
TNIP2	10.82±1.17	12.47±1.72	up	0.21	0.23	no
HDAC3	9.65±0.83	8.09±1.79	down	-0.26	0.23	no
BAX	30.51±1.63	26.73±0.40	down	-0.19	0.27	no
BCL2L11	1.24±0.19	1.60±0.86	up	0.37	0.30	no
SERPINH1	67.01±6.39	59.11±6.00	down	-0.18	0.31	no
TP53	14.32±3.94	16.64±5.57	up	0.22	0.36	no
NUFIP1	3.28±0.23	2.78±0.46	down	-0.24	0.36	no
NR2F6	6.34±0.66	5.47±0.52	down	-0.21	0.36	no
NFKBIE	5.49±0.23	6.14±0.17	up	0.16	0.37	no
HDAC1	21.36±1.67	19.08±1.76	down	-0.16	0.38	no
NR1H2	7.00±0.29	7.64±0.32	up	0.13	0.38	no
TRIM25	15.95±1.14	17.22±0.81	up	0.11	0.38	no
NFKBIZ	2.03±0.66	2.35±0.10	up	0.21	0.40	no
SIN3B	10.10±0.48	10.89±0.59	up	0.11	0.40	no
TGFBR1	2.24±0.05	2.52±0.60	up	0.17	0.41	no

CDKN1A	61.75±7.48	75.70±47.59	up	0.29	0.42	no
SIN3A	4.42±0.01	4.77±0.37	up	0.11	0.42	no
PARP16	1.22±0.10	1.40±0.10	up	0.19	0.46	no
RAC1	97.17±2.13	102.74±4.36	up	0.08	0.49	no
ENG	196.11±21.26	179.55±14.65	down	-0.13	0.50	no
NFKBIB	6.70±2.09	7.48±1.82	up	0.16	0.51	no
CDH2	9.06±1.49	8.21±0.70	down	-0.14	0.51	no
HRAS	17.27±1.03	15.71±1.87	down	-0.14	0.53	no
LCOR	1.38±0.31	1.50±0.41	up	0.12	0.54	no
CCND1	61.99±3.15	65.01±5.03	up	0.07	0.56	no
MDM2	15.71±1.00	16.48±1.48	up	0.07	0.56	no
PNO1	10.71±0.78	9.85±1.31	down	-0.12	0.58	no
BCL2L1	24.80±0.82	21.73±10.46	down	-0.19	0.58	no
PDCD1LG2	3.41±0.427	3.07±0.20	down	-0.15	0.61	no
RARB	11.78±1.20	12.37±1.86	up	0.07	0.62	no
RARG	2.27±0.30	2.09±0.04	down	-0.12	0.69	no
MYC	14.32±6.44	16.82±13.35	up	0.23	0.69	no
EHMT2	7.00±0.33	7.20±0.60	up	0.04	0.71	no
CDKN1B	13.27±0.30	13.67±1.32	up	0.04	0.72	no
APP	317.06±42.02	320.62±22.38	up	0.02	0.82	no
BAK1	16.47±1.64	15.81±0.67	down	-0.06	0.83	no
CYP1A1	14.44±1.14	14.54±1.36	up	0.01	0.85	no
CDK4	41.54±5.44	40.16±1.40	down	-0.05	0.86	no
ESRRA	5.97±0.47	5.70±1.76	down	-0.07	0.86	no
RB1	9.85±1.34	9.56±0.31	down	-0.04	0.89	no
NCOA1	3.57±0.23	3.57±0.12	up	0.001	0.90	no
PTEN	5.70±0.39	5.67±0.65	down	-0.01	0.95	no
NFKBIL1	6.23±0.82	6.21±0.52	down	-0.005	0.95	no
KAT2B	2.75±0.13	2.72±0.47	down	-0.02	0.98	no
SRSF2	13.87±1.03	13.70±2.23	down	-0.02	0.99	no
GTF3C1	14.23±1.03	14.01±1.38	down	-0.02	0.99	no

Table S5. The genes which interact with KLF6 (Node1). According to STRING analysis, totally 17 genes (Node2) directly interact with KLF6.

Node2	Co-expression	Experimentally determined interaction	Automated text mining	Combined score
JUN	0.785	0.101	0.685	0.934
SP1	0	0.846	0.874	0.878
ATF3	0.689	0.062	0.55	0.857
LCOR	0	0.281	0.65	0.738
TP53	0	0.226	0.644	0.713
SERPINH1	0	0.056	0.572	0.578
CCND1	0	0.056	0.534	0.541

PMAIP1	0.053	0.058	0.526	0.54
PTEN	0.053	0.059	0.498	0.514
NFKBIA	0.171	0.298	0.218	0.505
RELA	0.062	0.281	0.256	0.455
HDAC3	0	0.345	0.201	0.454
MYC	0.102	0.058	0.402	0.45
CXCL8	0.098	0.27	0.229	0.447
KLF4	0.119	0.27	0.73	0.417
CDKN1A	0.085	0.058	0.37	0.409
CCL2	0.052	0.27	0.212	0.407