

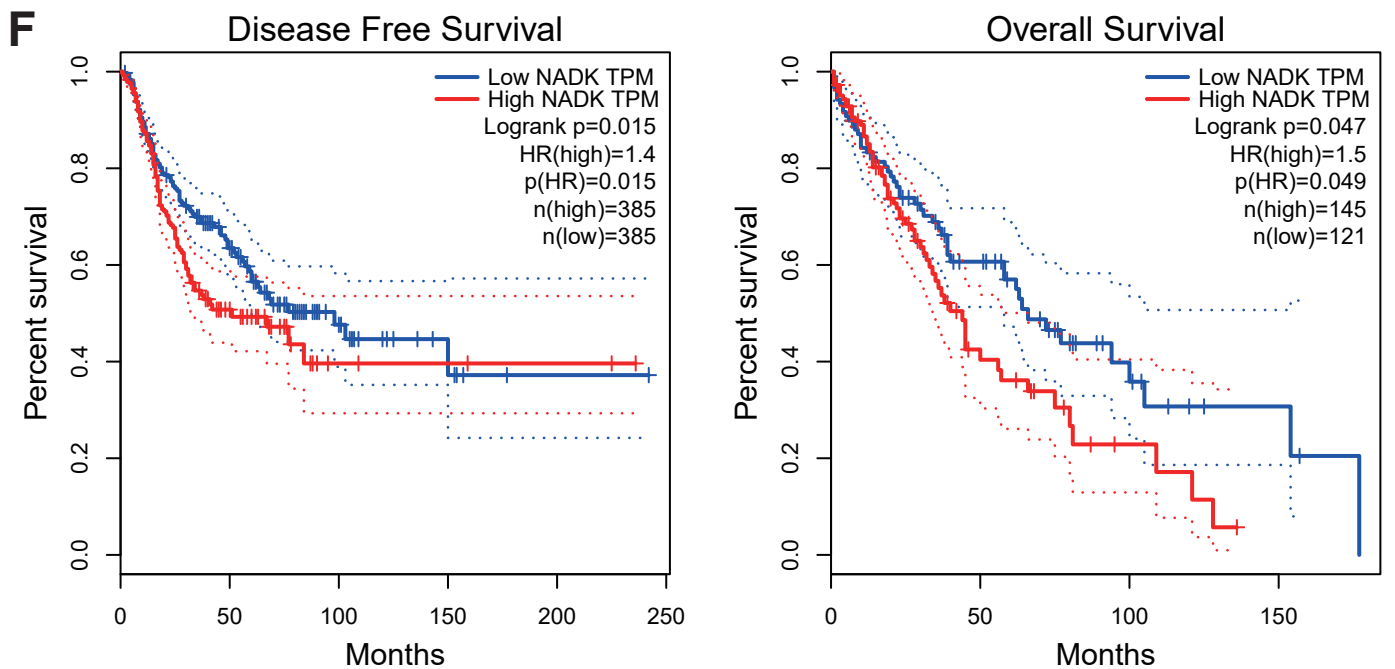
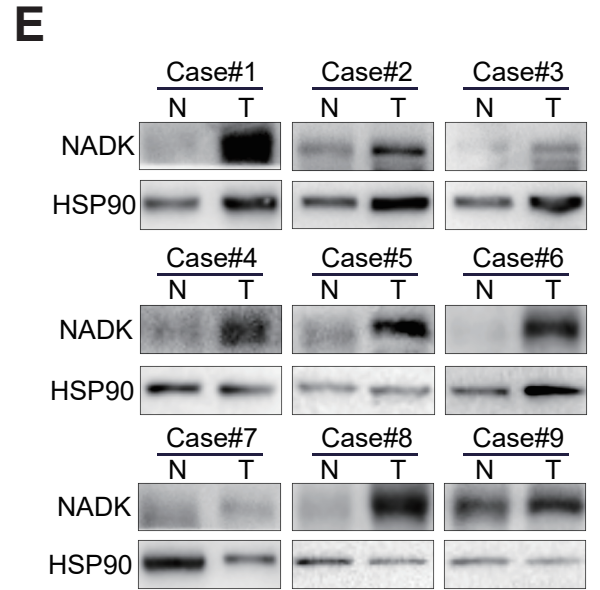
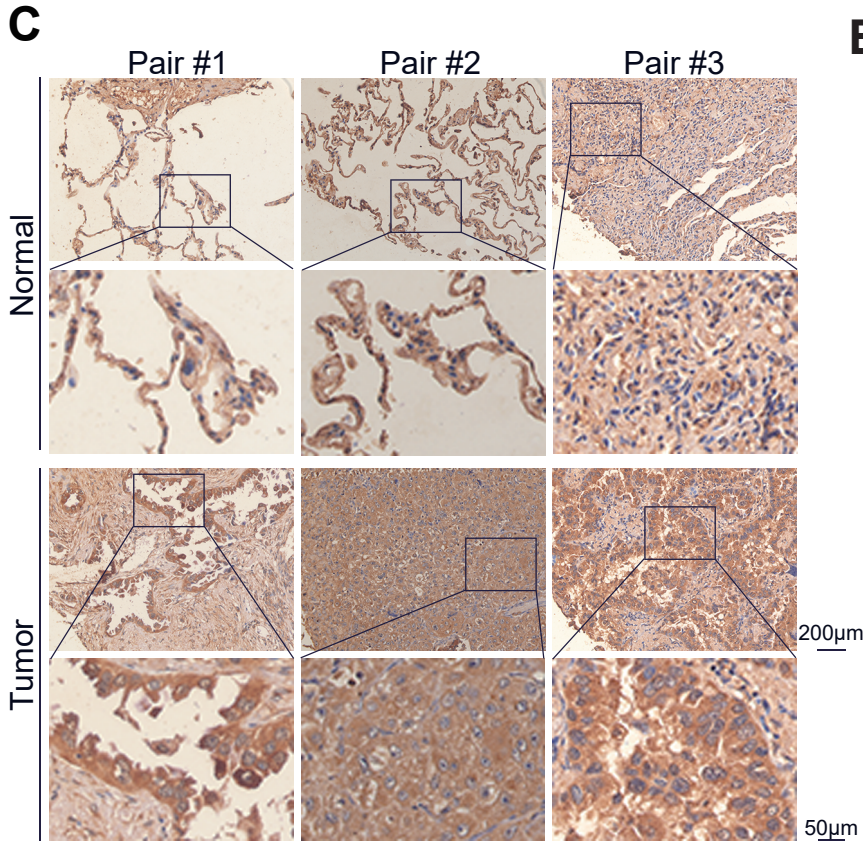
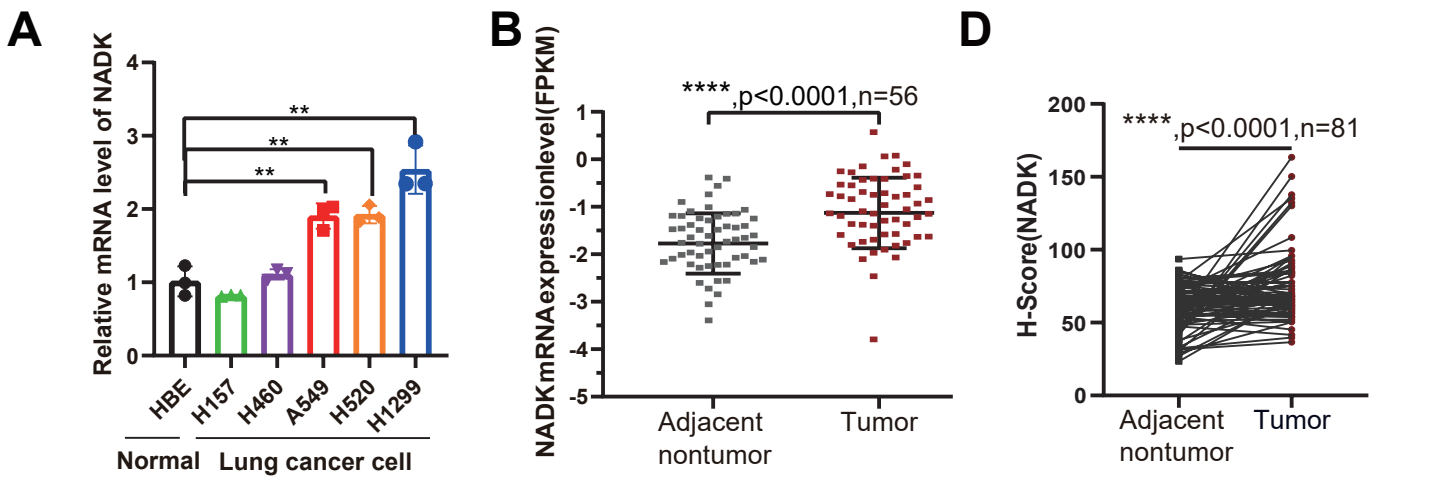
## Supplementary Materials

The supplementary materials included 6 figures and 3 tables.

### 1. Supplementary figures

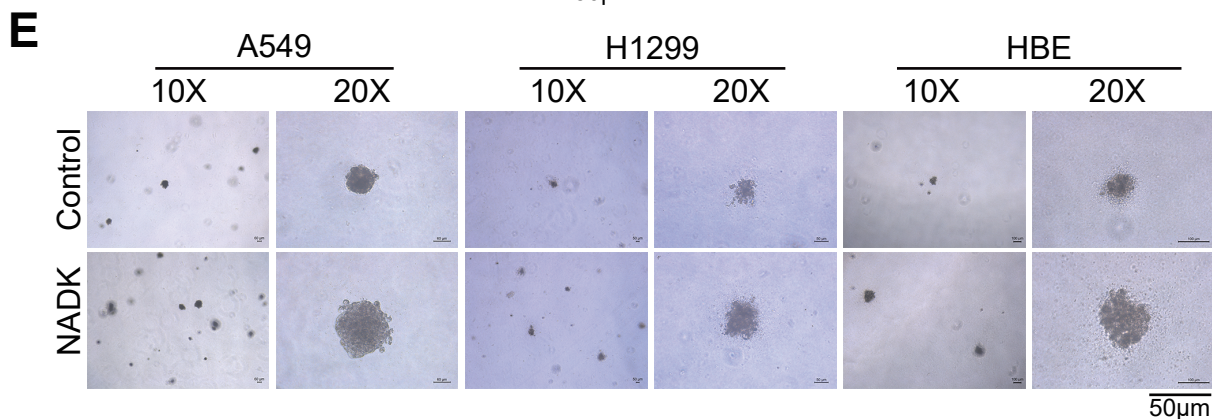
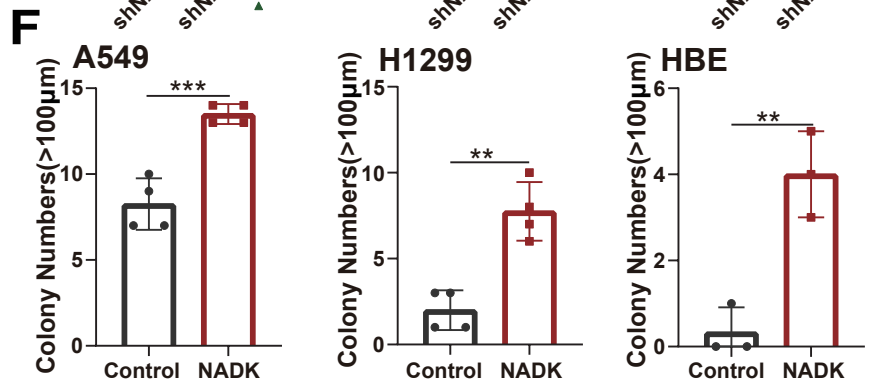
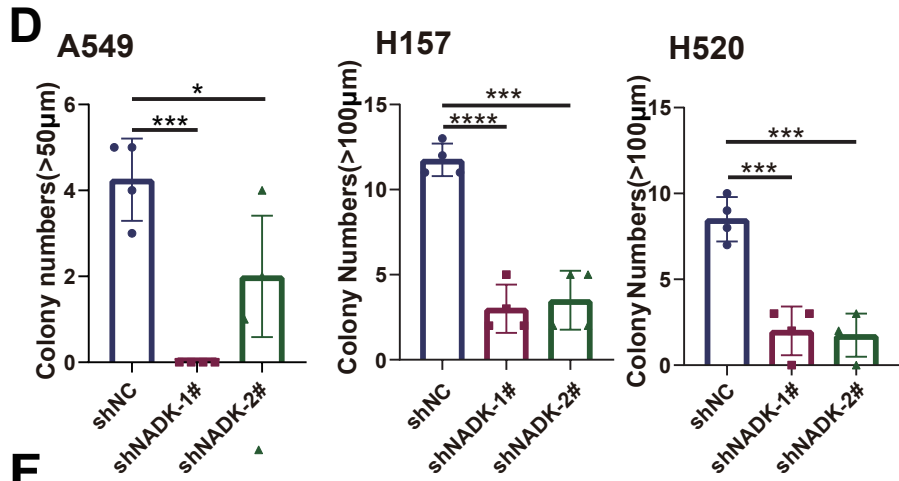
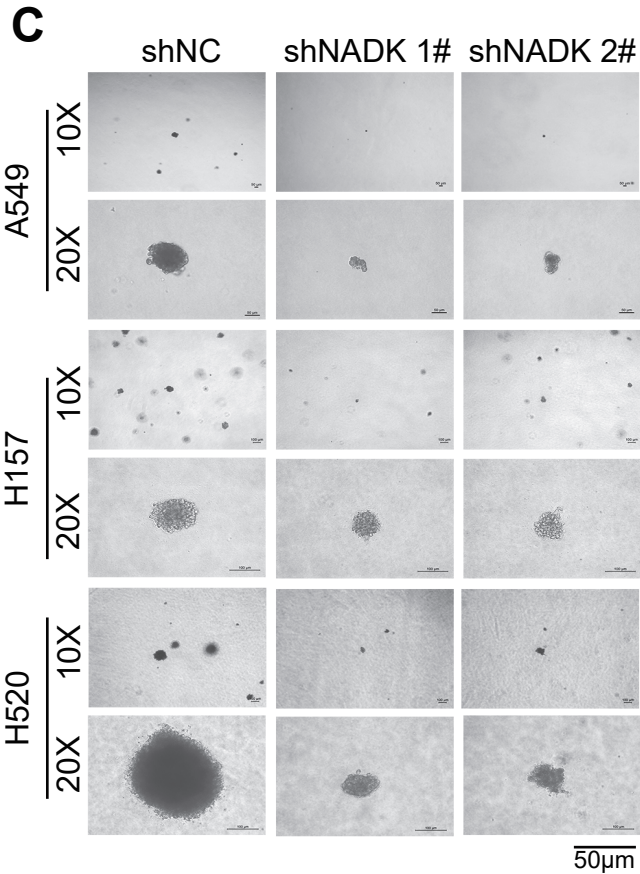
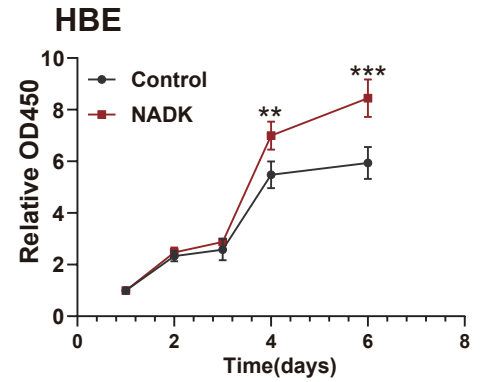
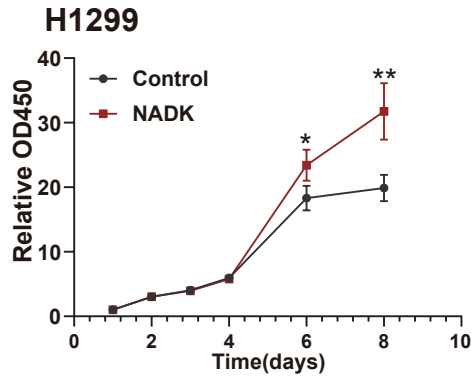
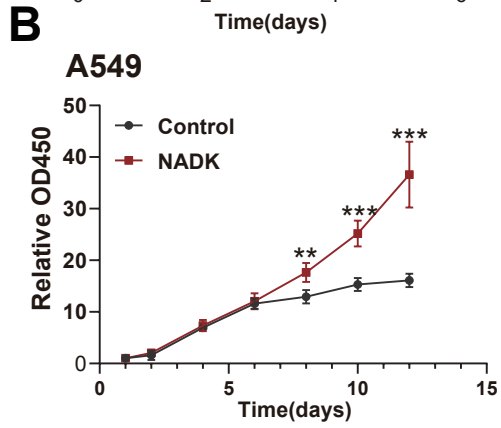
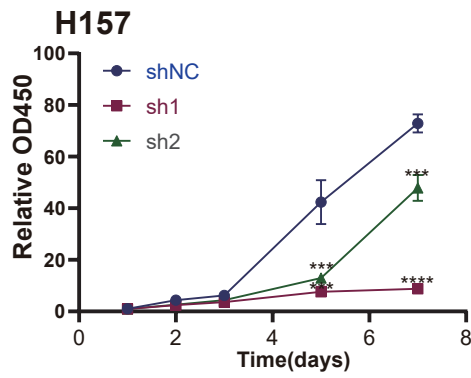
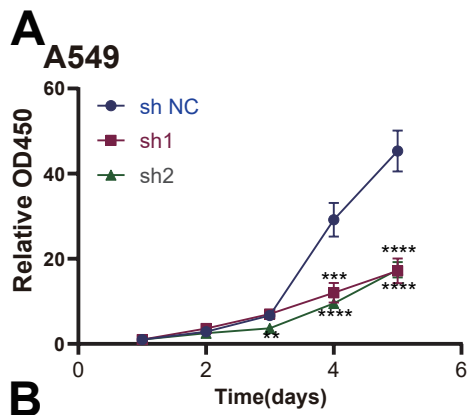
**Supplementary Figure 1. The expression of NADK is elevated in lung cancer.**

**Figure S1A.** Relative mRNA levels of NADK in human NSCLC cell (H157, H460, A549, H520 and H1299) and human bronchial epithelial cell (HBE) were analysed with a *t* test. **S1B.** The mRNA levels of NADK in 56 NSCLC tissues and paired adjacent tissues were analysed with a paired *t* test. **S1C and 1D.** Representative IHC images showing the expression of NADK in 3 NSCLC tissues and matched adjacent nontumor tissues. The protein levels of NADK in the NSCLC tissues were scored. The tissue array contained 81 NSCLC tissues and paired adjacent tissues (**S1D**). Paired *t* test was performed. **S1E.** Western blot was used to measure the levels of NADK protein in 9 NSCLC tissues and paired adjacent tissues. N, the adjacent nontumor tissue; T, the tumor tissue. HSP90 was used as the internal reference. **S1F.** The GEPIA database was used to analyse the correlation between the expression of NADK and the progression-free survival (PFS) of NSCLC patients (**Left**), Overall Survival (OS) (**Right**) of patients with LUSC. The scale bars were indicated. \*\*,  $P < 0.01$ ; \*\*\*\*,  $P < 0.0001$ .



**Supplementary Figure 2. NADK enhances proliferation and anchorage-independent growth of NSCLC cells.**

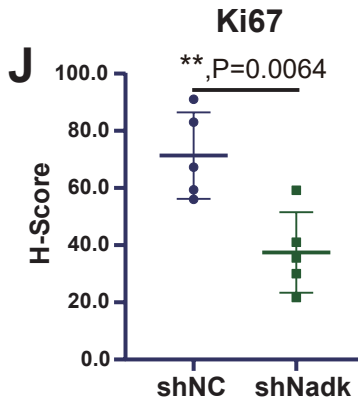
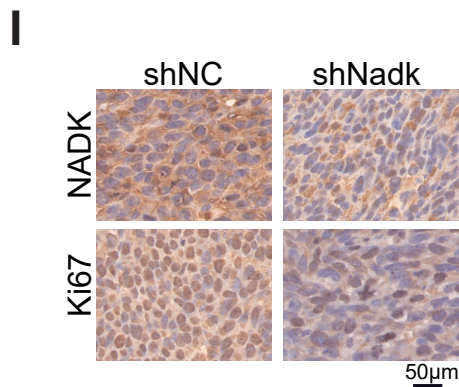
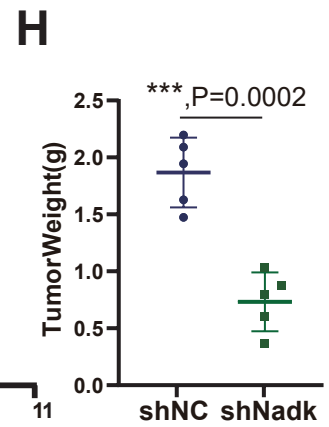
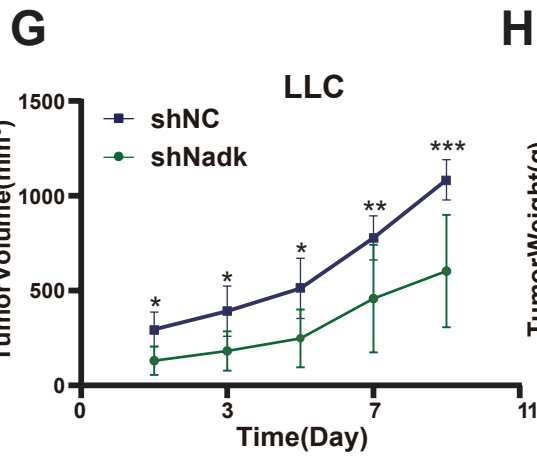
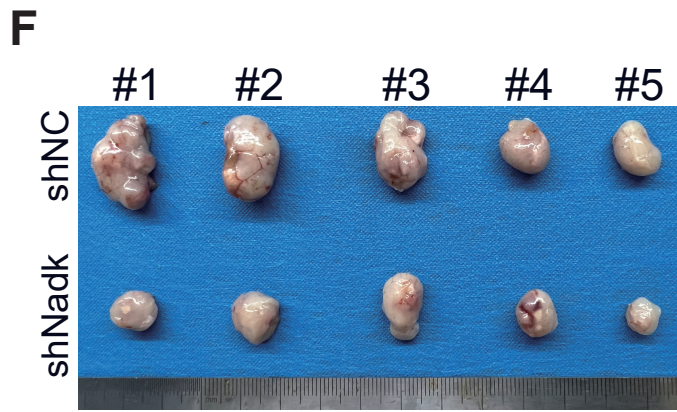
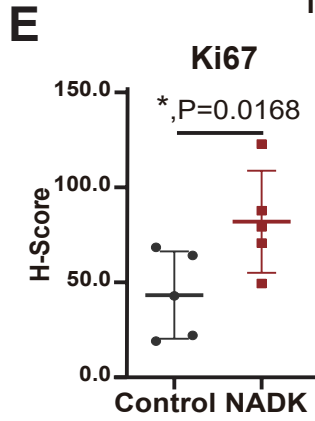
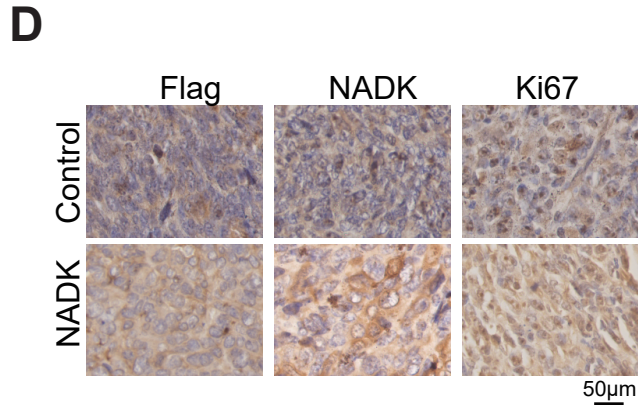
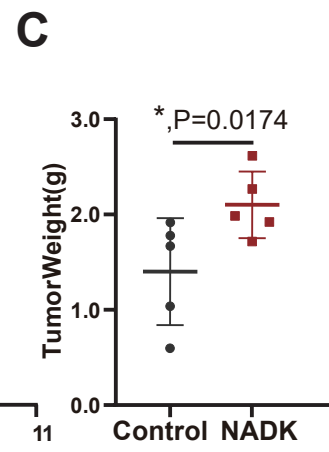
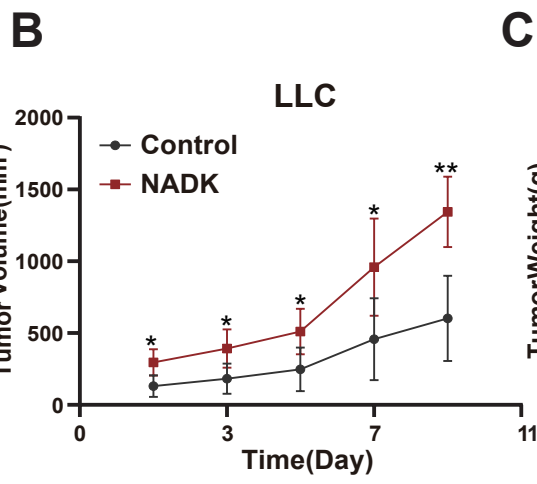
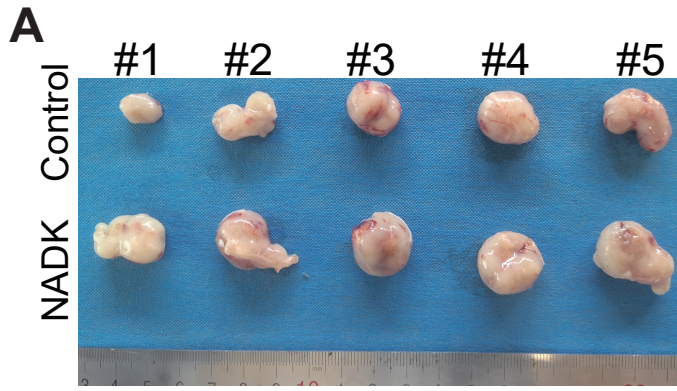
Figure **S2A**. A CCK8 assay was performed to detect the effects of NADK knockdown on the proliferation of A549 and H157 cells. **S2B**. The effects of overexpressed NADK on the proliferation of NSCLC cells (A549, H1299, HBE) were detected with the CCK8 assay. **S2C-D**. Soft-agar assay was used to measure the effects of NADK knockdown on the anchor-independent growth of A549, H157 and H520 cells. **S2E-F**. Soft-agar assay was performed to examine the effect of NADK overexpression on the colony formation of A549, H1299 and HBE cells (**S2E**). The colonies were quantified and analysed (**S2F**). The scale bars were indicated. \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ ; \*\*\*\*,  $P < 0.0001$ .





**Supplementary Figure 3. NADK promotes the tumorigenicity of NSCLC cells.**

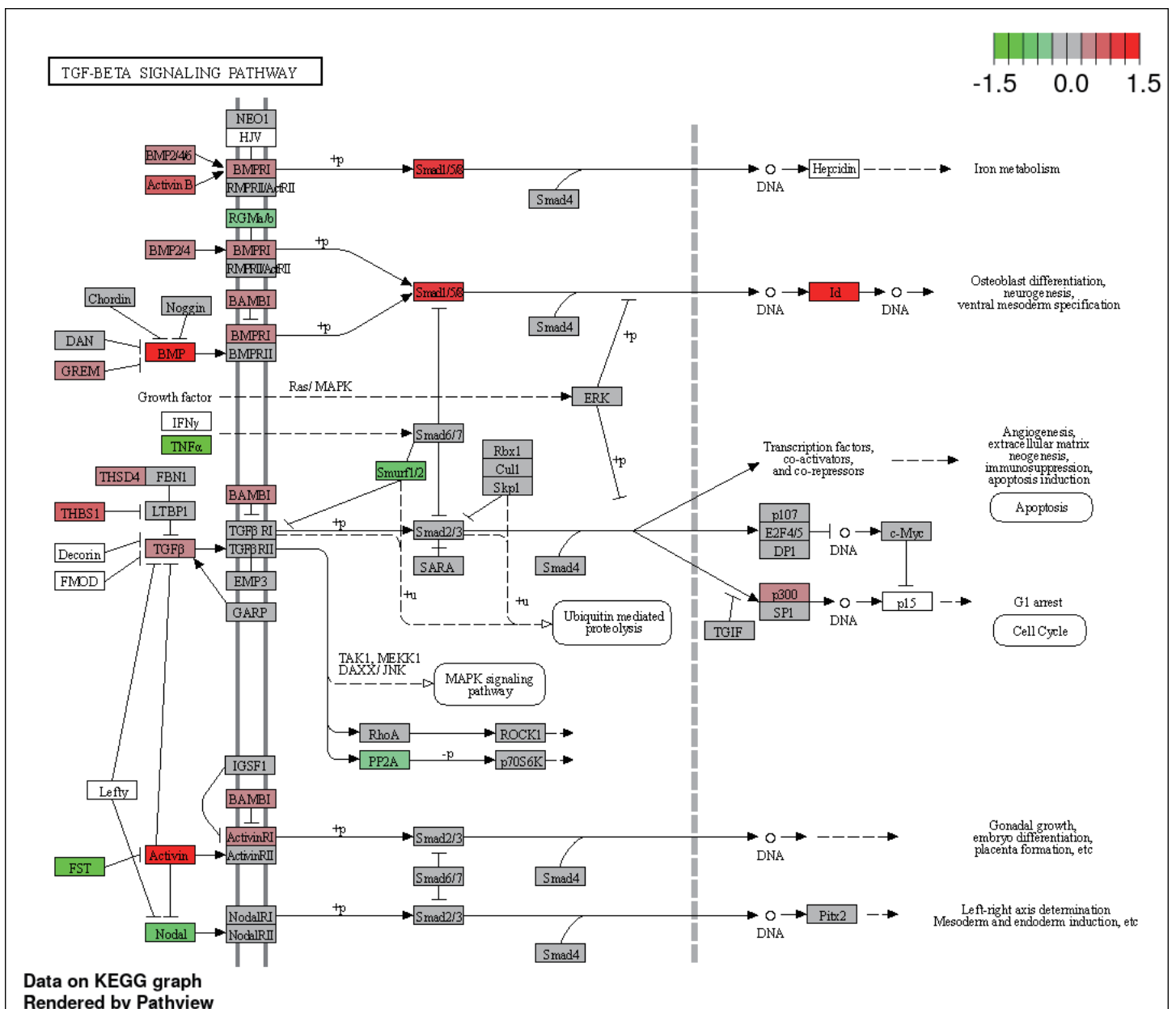
Figure **S3A**. The morphology of the xenografts formed by the LLC control cells or LLC cells with the overexpression of NADK. See “materials and methods” for details. **S3B**. Growth curve of xenografts shown in **S3A**. Tumor volumes were measured at indicate time points. (n=5, Error bars represent SEM, \*,  $P<0.05$ ; \*\*,  $P<0.01$ . Unpaired *t* test.) **S3C**. The weight of the xenografts in **S3A** was examined at the end of the experiment. **S3D -S3E**. Representative IHC images of Ki67 for xenografts **shown in S3A (S3D)**, the expression of Ki67 were scored and analysed (**S3E**). **S3F**. The morphology of the xenografts formed by the LLC cells infected with the NADK shRNA virus or the negative control shRNA virus. **S3G**. Growth curve of xenografts shown in **S3F**. Tumor volumes were measured at indicate time points. (n=5, Error bars represent SEM, \*,  $P<0.05$ ; \*\*,  $P<0.01$ . Unpaired *t* test). **S3H**. The weight of the xenografts shown in **S3F** was measured and analysed with unpaired *t* test. **S3I-S3J**. The expression of Ki67 in LLC-shNadk xenografts was examined by IHC, scored and analysed. The scale bars were indicated. \*,  $P<0.05$ ; \*\*,  $P<0.01$ ; \*\*\*,  $P<0.001$ ; \*\*\*\*,  $P<0.0001$ .



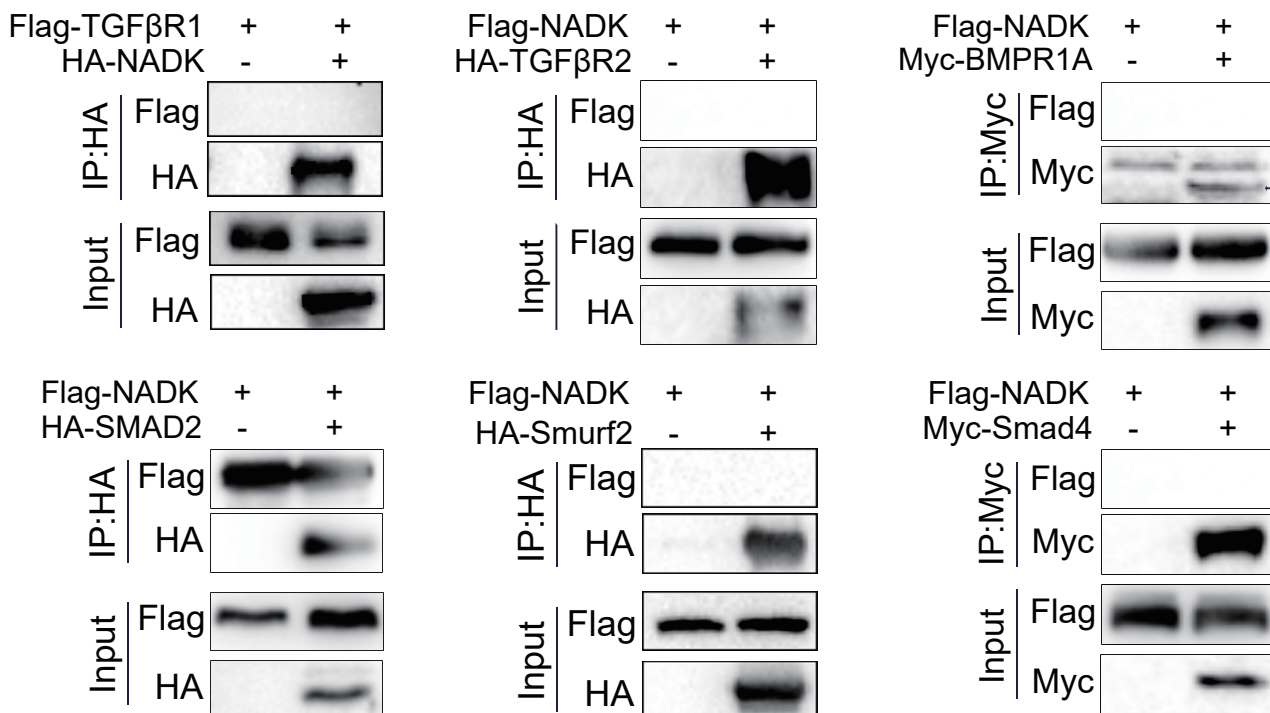
**Supplementary Figure 4. NADK activates TGF $\beta$  signalling.**

Figure **S4A**. KEGG pathview analysis shows the enrichment of TGF $\beta$  signalling in A549 cells with NADK overexpression. **S4B**. Co-IP was performed to examine the interaction between NADK and key components of TGF $\beta$  signalling.

**A**



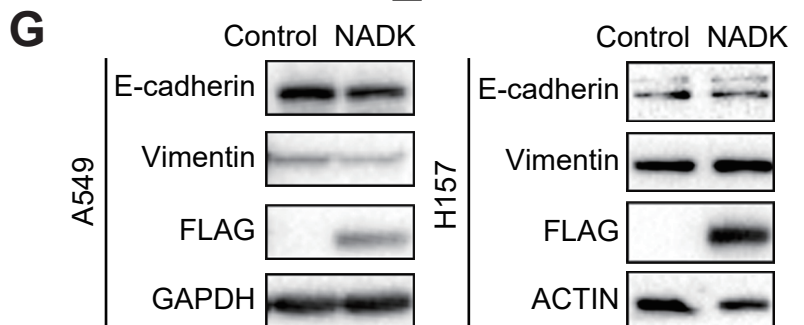
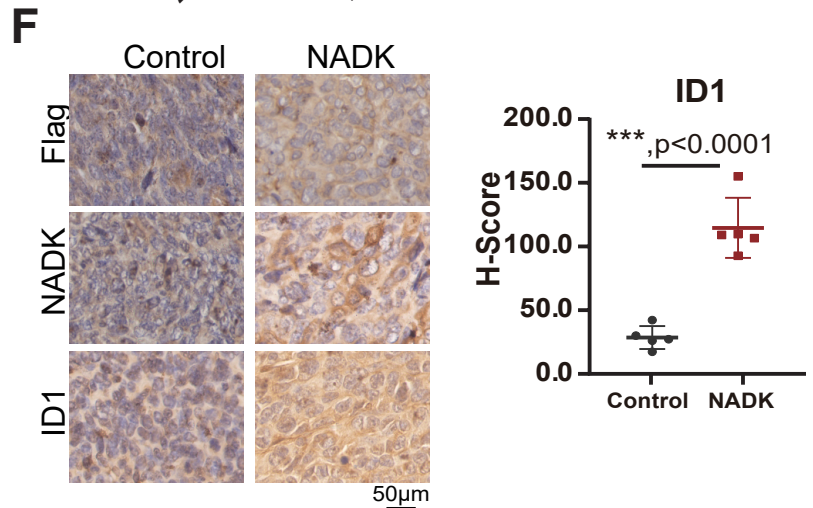
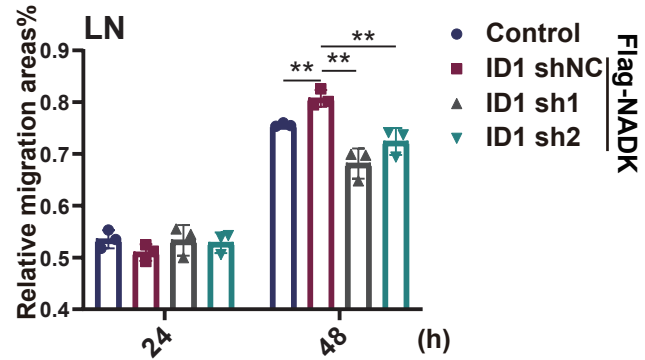
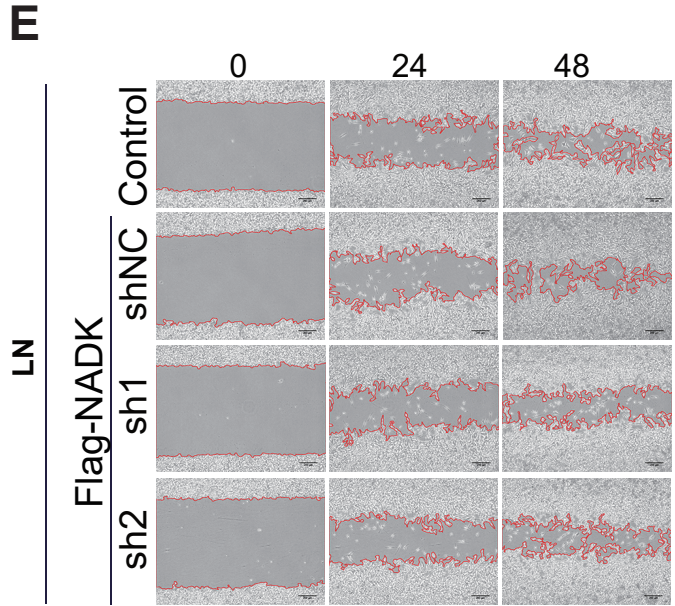
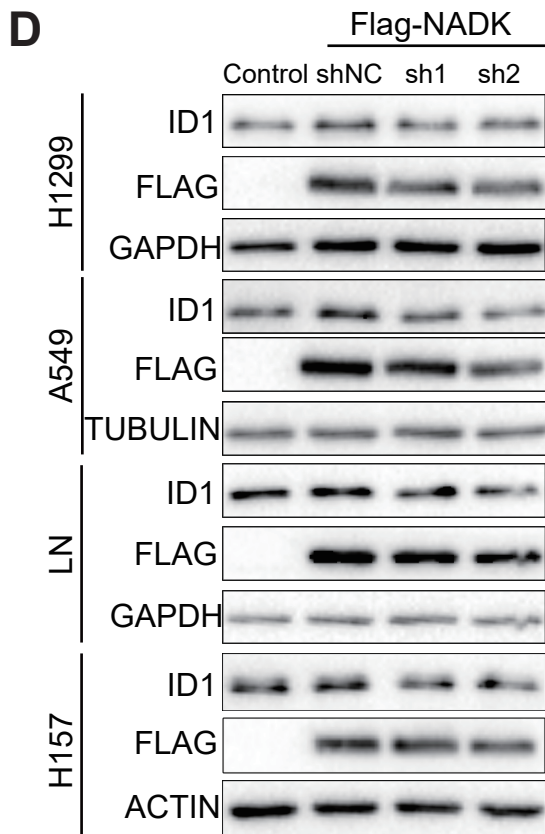
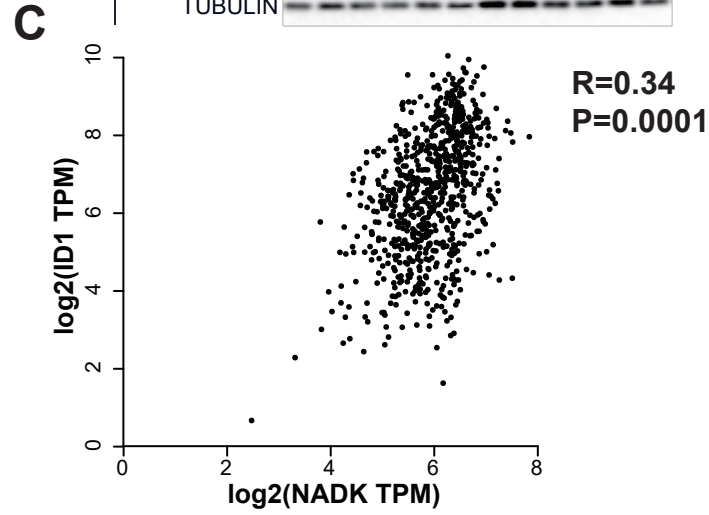
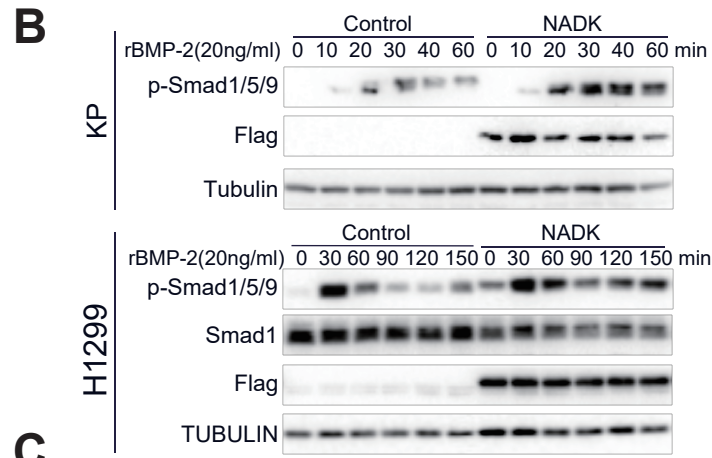
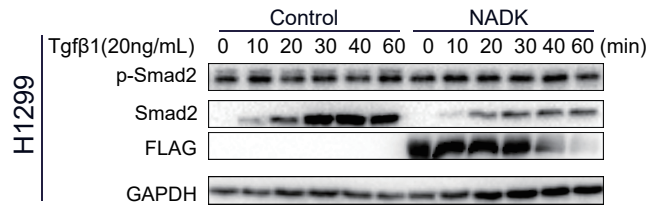
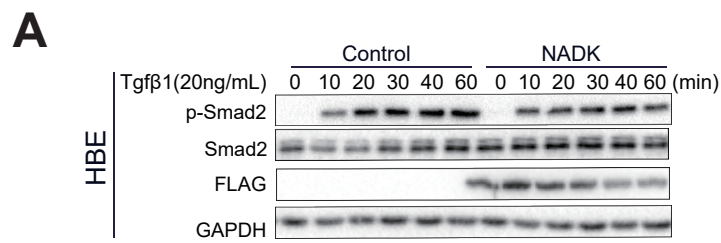
**B**



**Supplementary Figure 5. NADK activates BMPs/ID1 signaling axis.**

Figure **S5A**. Western blotting was used to detect the level of phosphorylated Smad2 in NADK overexpressed HBE and H1299 cells treated with TGF $\beta$ 1. **S5B**. Western blotting was performed to measure phosphorylation level of Smad1/5/9 after the treatment of BMP-2 in NADK overexpressed KP and H1299 cells. **S5C** Correlation analysis between ID1 mRNA level and NADK mRNA level in NSCLC sample after mining the TCGA and GTEx databases. **S5D**. Knockdown of ID1 in NADK overexpressed cell lines. **S5E**. Wound healing assay was used to detect the effect of ID1 knockdown on the migration promoted by NADK. Relative migration areas were measured and analysed. **S5F** IHC staining was performed to examine the levels of ID1 protein in xenografts formed by LLC cells overexpressed NADK and LLC control cells. The levels of ID1 protein were quantified and analysed. **S5G**. Western blot was performed to measure the level of EMT marker (E-Cadherin and Vimentin) in cells overexpressing NADK (A547 and H157). The scale bars were indicated. \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ .

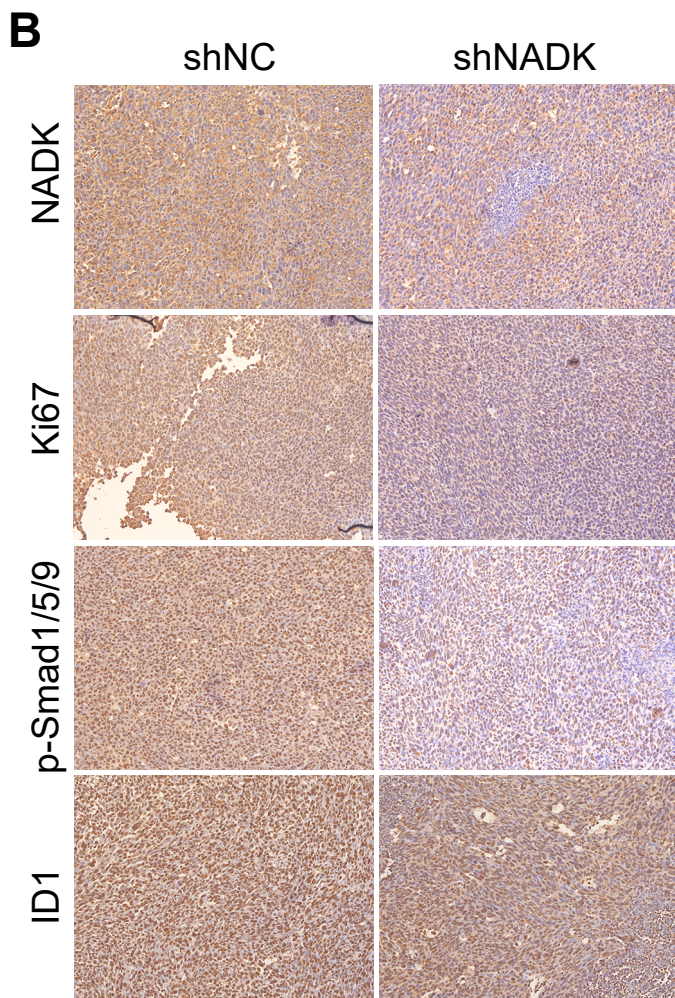
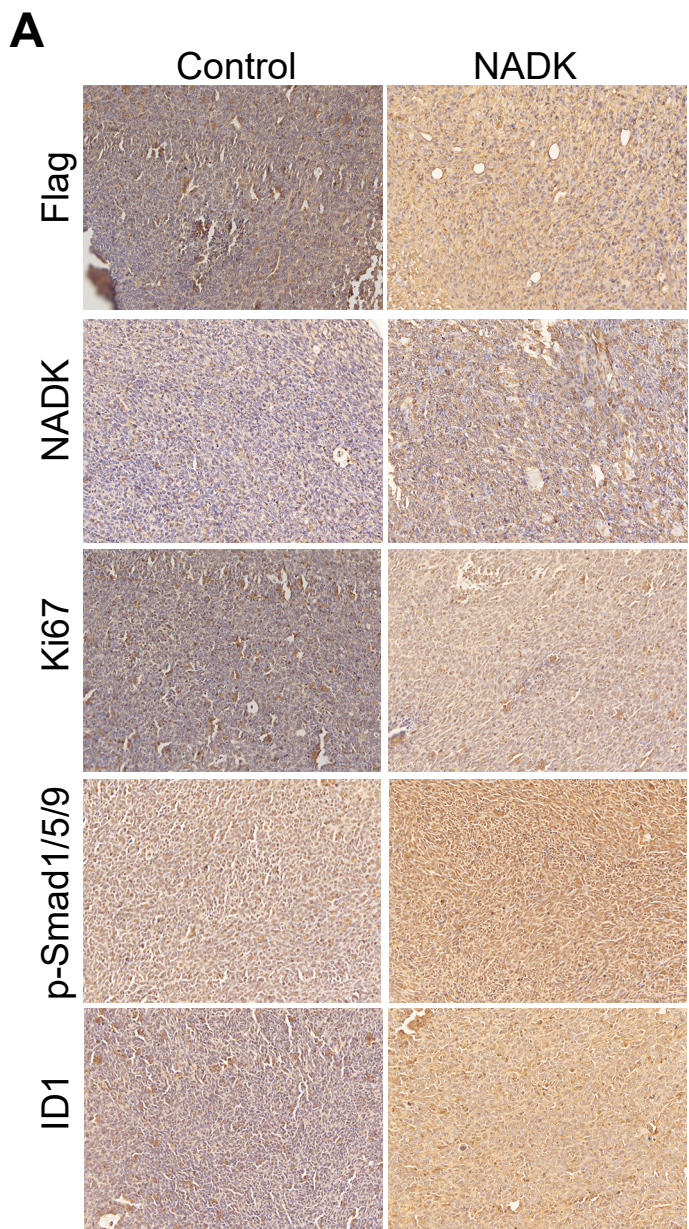




**Supplementary Figure 6. Expression of NADK, Ki67, p-Smad1/5/9 and ID1 in the xenografts were examined using IHC.**

Figure **S6A**. Representative IHC images of Flag, NADK, Ki67, p-Smad1/5/9 and ID1 performed on xenografts formed by cells overexpressing of NADK. **S6B**. Representative IHC images of NADK, Ki67, p-Smad1/5/9 and ID1 performed on xenografts formed by the cells with NADK knockdown.





## **2. Supplemental Table**

**Table S1.** Primers and oligo sequences.

**Table S2.** NSCLC tissue array and detail pathological information.

**Table S3.** KEGG Enrichment: A549 overexpressing NADK VS A549 Control cells.

**Supplementary Table 1 qPCR, shRNA and over-expression plasmid Primers Sequence**

Primer	Forward sequence (5'-3')	Reverse sequence (5'-3')
NADK (Homo)-qPCR	ACCTGAAGCAAGGAACACAGC	AGCGGGTAGCATGAGGTAGT
ID1 (Homo)-qPCR	CTGCTCTACGACATGAACGG	GAAGGTCCCTGATGTAGTCGAT
Id1 (Mouse)-qPCR	CCTAGCTGTTCGCTGAAGGC	CTCCGACAGACCAAGTACCAC
Actin (Homo)-qPCR	GAATCAATGCAAGTTCGGTTCC	TCATCTCCGCTATTAGCTCCG
Gapdh (Mouse)-qPCR	AGGTCGGTGTGAACGGATTTG	TGTAGACCATGTAGTTGAGGTCA
NADK shRNA 1#	CCGGGCATTGGAACGTCGGAA GAACTCGAGTTCTTCCGGACGTT CCAATGCTTTTTG	AATTCAAAAAGCATTGGAACGT CCGGAAGAAGCTCGAGTTCTTCC GGACGTTCCAATGC
NADK shRNA 2#	CCGGGCATCAGCATCACTACCTC ATCTCGAGATGAGGTAGTGATGC TGATGCTTTTTG	AATTCAAAAAGCATCAGCATCA CTACCTCATCTCGAGATGAGGTA GTGATGCTGATGC
Nadk shRNA (Mouse)	CACCGTTTCATCACTCACTATAGC A	AAACTGCTATAGTGAGTGATGA AAC
ID1 shRNA 1#	GATCCGACTCGGAATCCGAAGTT GGAATTCAAGAGATTCCAACCTC GGATTCCGAGTTTTTTTTG	AATTCAAAAAACTCGGAATCC GAAGTTGGAATCTCTTGAATTCC AACTTCGGATTCCGAGTCG
ID1 shRNA 2#	GATCCGGCAGGTAAACGTGCTGC TCTATTCAAGAGATAGAGCAGCA CGTTTACCTGCTTTTTTTG	AATTCAAAAAAGCAGGTAAACG TGCTGCTCTATCTCTTGAATAGA GCAGCACGTTTACCTGCCG
Id1 shRNA 1#(Mouse)	GATCCGGCATGTGTTCCAGCCGA CGATTCAAGAGAATCGTCGGCT GGAACACATGCTTTTTTTG	AATTCAAAAAAGCATGTGTTCC AGCCGACGATTCTCTTGAAATCG TCGGCTGGAACACATGCCG
Id1 shRNA 2#(Mouse)	GATCCGGCGAGGTGGTACTTGGT CTGTTTCAAGAGAACAGACCAA GTACCACCTCGTTTTTTTTG	AATTCAAAAAAGCGAGGTGGTA CTTGGTCTGTTCTCTTGAAACAG ACCAAGTACCACCTCGCCG
FLAG-NADK	AAGCTGGGCGGTGGTGGATCCAT GGAGATGGAGCAGGAGA	TGCACCGGTACTAGTTCTAGATC AGCCCTCCTCCTCCTCT
FLAG-NADK TD1	AAGCTGGGCGGTGGTGGATCCAT GGAGATGGAGCAGGAGA	TGCACCGGTACTAGTTCTAGACT ACAGCACGCTCTTAGGGG
FLAG-NADK TD2	AAGCTGGGCGGTGGTGGATCCGT CATCAAGAAGATGAGGGAC	TGCACCGGTACTAGTTCTAGACT AGTTGCCCTCGATGACCTG
FLAG-NADK TD3	AAGCTGGGCGGTGGTGGATCCG CCGCCGTGGTGTGAGAAG	TGCACCGGTACTAGTTCTAGATC AGCCCTCCTCCTCCTCT



**Supplementary Table 2 NSCLC tissues array and detail pathological information**

Number	H-score	Gender	Age	Total LM	Positive LN	LN Rate	T	N	M	TNM stage	AJCC stage, 7th edition	Pathological grade	Tumor size (cm <sup>3</sup> )	Survival time (Month)	Survival status
E05A0031	150.2	Male	47	10	10	1	T2a	N1	M0	2b	2A	II	42.875		Lost
E05A0032	90.8	Female	72	3	0	0	T1b	N0	M0	1a2	1A	II	9	78	Death
E05A0036	135.2	Female	59	15	14	0.933333	T3	N1	M0	3a	3A	II	45.6	38	Death
E05A0046	130	Female	66	12	9	0.75	T2a	Nx	M0	2-3	2-3	II	36	49	Death
E05A0059	87.2	Male	60	3	0	0	T2b	N0	M0	2a	2A	III	72		Lost
E05A0060	41.6	Male	49	1	0	0	T1b	N0	M0	1a2	1A	II	18	116	Alive
E05A0064	45.2	Male	66	10	0	0	T3	N0	M0	2B	2B	I-II	180		lost
E05A0081	67.8	Female	53	5	0	0	T1b	N0	M0	1a2	1A	II	18	113	Alive
E05A0104	132.2	Male	74	9	1	0.111111	T2a	Nx	M0	2-3	2-3	II	8.37333333	33	Death
E05A0123	95.2	Male	74	2	0	0	T2a	N0	M0	1a1	1B	II	14	21	Death
E05A0131	60	Female	20	8	0	0	T1b	N0	M0	1a2	1A	II-III	12		lost
E05A0142	95.8	Male	58	11	0	0	T2a	N0	M0	1b	1B	II-III	24	39	Death
E05A0146	95.2	Male	30	10	0	0	T1b	N0	M0	1a2	1A	II-III	18	34	Death
E05A0149	163.4	Male	67	20	14	0.7	T2b	Nx	M0	2-3	2-3	III	180	39	Death
E05A0172	95.2	Male	57	12	0	0	T2a	N0	M0	1b	1B	II-III	55.125		lost
E05A0175	137.6667	Female	25	7	1	0.142857	—	Nx	M0	2-3	2-3	III	140	103	Alive
E05A0182	92.6	Female	64	8	0	0	T2a	N0	M0	1b	1B	II	24	15	Death
E05A0195	72.8	Female	50	5	4	0.8	T3	N1	M0	3a	3A	I	15	55	Death
E05A0197	69	Female	46	13	3	0.230769	T3	N1	M0	3a	3A	III	346.5	10	Death

**Supplementary Table 2 NSCLC tissues array and detail pathological information**

Number	H-score	Gender	Age	Total LM	Positive LN	LN Rate	T	N	M	TNM stage	AJCC stage, 7th edition	Pathological grade	Tumor size (cm <sup>3</sup> )	Survival time (Month)	Survival status
E05A0201	68	Male	60	10	0	0	T2a	N0	M0	1b	1B	II	49	62	Death
E05A0208	60.6	Male	47	7	1	0.142857	T3	N1	M0	3a	3A	III	180	33	Death
E05A0209	70.5	Male	65	18	15	0.833333	T3	N2	M0	3b	3A	III	204	14	Death
E05A0210	60.6	Female	58	12	0	0	T2a	N0	M1b	4a	2-3	II-III	63	49	Death
E05A0211	70.5	Female	67	5	1	0.2	T2a	N1	M0	2b	2A	II	26.25	13	Death
E05A0222	64.4	Male	57	11	0	0	T1b	N0	M0	1a2	1A	II	9.42		lost
E05A0226	63.6	Female	55	15	0	0	T1b	N0	M0	1a2	1A	I	18.75		lost
E05A0238	84.2	Male	51	15	2	2	—	Nx	M0	2-3	2-3	II	18		lost
E05A0252	64.8	Female	50	4	0	0	T1b	N0	M0	1a2	1A	II	22.5	92	Alive
E05A0255	68.6	Female	68	8	0	0	T1b	N0	M0	1a2	1A	II	7.2	91	Alive
E05A0270	63.6	Male	55	8	0	0	T2a	N0	M0	1b	1B	II-III	36	91	Alive
E05A0272	59.6	Female	76	1	0	0	T1b	N0	M0	1a2	1A	II-III	12	15	Death
E05A0273	36.6	Female	56	6	0	0	T1	N0	M0	1a2	1A	II	1.04666667		lost
E05A0274	50.4	Female	62	25	11	0.44	T3	N3	M0	3c	3B	II-III	10.5	9	Death
E05A0277	60.6	Male	74	5	2	0.4	T3	N1	M0	3a	3A	III	200	10	Death
E05A0279	56	Male	49	9	4	0.444444	T2a	N2	M0	3a	3A	II	36	17	Death
E05A0280	95.2	Male	73	13	3	0.230769	T2b	N1	M0	2b	2B	II	86.625	33	Death
E05A0289	63.33333	Male	75	7	1	0.142857	T2a	N1	M0	2b	2A	II	10	59	Death
E05A0310	77.6	Female	69	4	1	0.25	T2a	Nx	M0	2-3	2-3	I-II	18	48	Death

**Supplementary Table 2 NSCLC tissues array and detail pathological information**

Number	H-score	Gender	Age	Total LM	Positive LN	LN/M Rate	T	N	M	TNM stage	AJCC stage, 7th edition	Pathological grade	Tumor size (cm <sup>3</sup> )	Survival time (Month)	Survival status
<b>E05A0317</b>	87.8	Female	57	12	10	0.83333333	T4	N2	M0	3b	3B	II-III	60	3	Death
<b>E05A0318</b>	90.4	Male	75	9	0	0	T4	N0	M0	3a	3A	II	48	27	Death
<b>E05A0321</b>	66.33333	Female	52	14	12	0.8571429	T3	N3	M0	3c	3B	II-III	5	44	Death
<b>E05A0332</b>	67.8	Male	55	4	0	0	T2a	N0	M0	1b	1B	II-III	49	87	Alive
<b>E05A0333</b>	75	Male	65	9	2	0.22222222	T2a	N1	M0	2b	2A	II	6	25	Death
<b>E05A0347</b>	66.4	Male	74	12	0	0	T2a	N0	M0	1b	1B	II	18.75	56	Death
<b>E05A0349</b>	54.8	Male	60	1	0	0	T2a	N0	M0	1b	1B	II	61.25	67	Death
<b>E05A0353</b>	101.75	Female	51	3	3	1	T1a	N2	M0	3a	3A	II	6	29	Death
<b>E05A0355</b>	66.6	Male	53	8	5	0.625	T2a	N2	M0	3a	3A	II	4	16	Death
<b>E05A0359</b>	88.8	Male	66	12	3	0.25	T2a	N1	M0	2b	2A	III	20	6	Death
<b>E05A0364</b>	77.4	Female	65	9	0	0	T2a	N0	M0	1b	1B	II	18	14	Death
<b>E05A0369</b>	50.25	Male	42	8	1	0.125	T1b	Nx	M0	2-3	2-3	II	12.5	13	Death
<b>E05A0392</b>	50.6	Female	57	4	2	0.5	T2a	Nx	M0	2-3	2-3	II	31.5	40	Death
<b>E05A0396</b>	53.2	Female	71	14	0	0	T1b	N0	M0	1a2	1A	II	9	84	Alive
<b>E05A0399</b>	60.2	Female	51	13	6	0.4615385	T2a	Nx	M0	2-3	2-3	II-III	36	57	Death
<b>E05A0403</b>	108.4	Male	64	7	2	0.2857143	T2a	N1	M0	2b	2A	II-III	12.5	83	Alive
<b>E05A0426</b>	66.75	Male	71	9	4	0.4444444	T3	N1	M0	3a	3A	II	36	33	Death
<b>E05A0448</b>	66.4	Female	60	16	8	0.5	T3	N3	M0	3c	3B	II	510	40	Death
<b>E05A0449</b>	85	Male	61	10	9	0.9	T2b	N3	M0	3b	3B	II-III	214.5	15	Death

**Supplementary Table 2 NSCLC tissues array and detail pathological information**

Number	H-score	Gender	Age	Total LM	Positive LN	LN Rate	T	N	M	TNM stage	AJCC stage, 7th edition	Pathological grade	Tumor size (cm <sup>3</sup> )	Survival time (Month)	Survival status
E05A0450	57.4	Female	58	6	0	0	T3	N0	M0	2b	2B	I-II	12.5	80	Alive
E05A0456	86	Female	62	11	9	0.8181818	T1a	Nx	M0	2-3	2-3	I-II/II-III	6	72	Death
E05A0463	57.2	Female	58	8	0	0	T3	N0	M0	2b	2B	I	560	35	Death
E05A0464	84.2	Male	60	7	1	0.1428571	T3	N1	M0	3a	3A	II	270	79	Alive
E05A0471	65.6	Male	63	10	3	0.3	T3	N2	M0	3b	3A	II	48	25	Death
E05A0475	58.5	Male	63	3	3	1	T2a	N1	M0	2b	2A	II	7.2	49	Death
E05A0482	63.5	Male	61	10	0	0	T2a	N0	M0	1b	1B	II-III	2	39	Death
E05A0486	85.4	Female	81	1	1	1	T2a	N1	M0	2b	2A	II	47.25	58	Death
E05A0502	83.6	Male	61	17	0	0	T2b	N0	M0	2a	2A	III	165.416	7	Death
E05A0519	69.75	Male	65	15	6	0.4	T2a	N2	M0	3a	3A	II-III	48	75	Alive
E05A0520	62	Male	74			#DIV/0!	T1a	—	M0	1a	1a	II	2	1	Death
E05A0523	54.2	Male	64	2	1	0.5	T2a	N1	M0	2b	2A	II	49	74	Alive
E05A0537	67.8	Male	53	13	0	0	T2a	N0	M0	1b	1B	III	36	52	Death
E05A0546	63.6	Female	73	5	4	0.8	T4	N2	M0	3b	3B	II	26.25	54	Death
E05A0550	77.8	Male	52	6	6	1	T2a	N2	M0	3a	3A	II	36.75	14	Death
E05A0565	54.8	Male	55	19	7	0.3684211	T2b	N2	M0	3b	3A	II-III	168	12	Death
E05A0575	76.4	Female	73	14	10	0.7142857	T2b	Nx	M0	2-3	2-3	II	157.5	12	Death
E05A0580	99.6	Male	44	6	1	0.1666667	T3	Nx	M0	2-3	2-3	II	180	3	Death
E05A0584	68	Female	50	3	0	0	T1a	N0	M0	1a2	1A	II	2.25	15	Death

**Supplementary Table 2 NSCLC tissues array and detail pathological information**

Number	H-score	Gender	Age	Total LM	Positive LN	LN Rate	T	N	M	TNM stage	AJCC stage, 7th edition	Pathological grade	Tumor size (cm <sup>3</sup> )	Survival time (Month)	Survival status
E05A0592	39.8	Female	60	21	0	0	T2b	N0	M0	2a	2A	II	160.875	2	Death
E05A0594	69.6	Male	54	3	3	1	T4	N2	M0	3b	3B	II-III	96	2	Death
E05A0595	59.75	Female	54	7	2	0.2857143	T3	N1	M0	3a	3A	II	7.5	29	Death
E05A0596	68.6	Female	48	14	0	0	T3	N0	M0	2b	2B	II	24.5	68	Alive
E05A0616	86.4	Male	59	13	10	0.7692308	T2a	N3	M0	3b	3B	III	26.25	2	Death
E05A0622	52	Male	78	6	0	0	T1b	N0	M0	1a2	1A	II	6.3	39	Death
E05A0627	75.4	Male	59	38	21	0.5526316	T2a	Nx	M0	2-3	2-3	II	48	25	Death
E05A0633	82.33333	Male	58	28	0	0	T2a	N0	M0	1b	1B	III	72	68	Alive
E05A0639	75	Female	56	9	4	0.4444444	T4	N2	M0	3b	3B	II	31.5	15	Death
E05A0640	63.2	Female	53	4	0	0	T2a	N0	M0	1b	1B	I-II	61.25	67	Alive
E05A0648	85	Female	62	6	1	0.1666667	T1b	Nx	M0	2-3	2-3	II	15	10	Death
E05A0659	63.4	Male	72	17	11	0.6470588	T2a	N2	M0	3a	3A	II	40	30	Death
E05A0663	61.66667	Male	84	9	0	0	T2b	N0	M0	2a	2A	I-II	110	24	Death
E05A0671	53.8	Male	61	19	0	0	T2b	N0	M0	2a	2A	II-III	137.5	65	Alive
E05A0677	77.8	Female	67	19	10	0.5263158	T1b	Nx	M0	2-3	2-3	II	12.5	64	Alive
E05A0682	56	Female	65	5	0	0	T2a	N0	M0	1b	1B	II	36	55	Death
E05A0699	89.8	Male	65	11	2	0.1818182	T3	N2	M0	3b	3A	III	84	8	Death
E05A0702	66.2	Male	65	15	0	0	T3	N0	M0	2b	2B	III	96.25	64	Alive
E05A0703	70.6	Female	77	12	8	0.6666667	T3	N3	M0	3c	3B	II	12.5	29	Death



**Supplementary Table 2 NSCLC tissues array and detail pathological information**

<b>Number</b>	<b>H-score</b>	<b>Gender</b>	<b>Age</b>	<b>Total LM</b>	<b>Posotive LN</b>	<b>LN Rate</b>	<b>T</b>	<b>N</b>	<b>M</b>	<b>TNM stage</b>	<b>AJCC stage, 7th edition</b>	<b>Pathological grade</b>	<b>Tumor size (cm<sup>3</sup>)</b>	<b>Survival time (Month)</b>	<b>Survival status</b>
<b>E05A0721</b>	70.6	Male	50	3	0	0	T2a	N0	M0	1b	1B	III	36		lost
<b>E05A0726</b>	67.8	Female	66	5	0	0	T2a	N0	M0	1a1	1B	I	15	62	Alive

### Supplementary Table 3 KEGG Enrichment: A549 NADK VS. A549 Control

Direction	GSEA analysis: NA vs EV	NES	Genes	adj.Pval
Down	TNF signaling pathway	-2.6055	86	1.3e-02
	NF-kappa B signaling pathway	-2.5939	70	1.3e-02
	Legionellosis	-2.5621	34	3.2e-02
	Rheumatoid arthritis	-2.4935	39	5.2e-02
	IL-17 signaling pathway	-2.489	57	5.2e-02
	Epithelial cell signaling in Helicobacter pylori infection	-2.4637	54	6.0e-02
	Viral protein interaction with cytokine and cytokine receptor	-2.4088	20	3.3e-02
	NOD-like receptor signaling pathway	-2.382	107	3.5e-02
	Kaposi sarcoma-associated herpesvirus infection	-2.3437	125	3.3e-02
	Cytokine-cytokine receptor interaction	-2.3315	86	6.7e-02
	Lipid and atherosclerosis	-2.2154	130	6.4e-02
	RIG-I-like receptor signaling pathway	-2.214	40	7.1e-02
	Influenza A	-2.1936	93	8.6e-02
	Epstein-Barr virus infection	-2.1916	131	6.7e-02
	Pertussis	-2.1795	39	7.1e-02
	C-type lectin receptor signaling pathway	-2.1734	65	8.6e-02
	Osteoclast differentiation	-2.143	71	8.6e-02
	Toll-like receptor signaling pathway	-2.1227	55	8.6e-02
	Measles	-2.1203	84	8.9e-02
	Tuberculosis	-2.0981	98	9.1e-02
	Leishmaniasis	-2.0952	34	7.0e-02
	Chagas disease	-2.0548	65	8.6e-02
	Amoebiasis	-1.9788	58	8.6e-02
	Chemokine signaling pathway	-1.9578	101	9.7e-02
	Ferroptosis	-1.9467	32	7.0e-02
	Hepatitis C	-1.9376	103	9.7e-02
	Small cell lung cancer	-1.9366	79	8.8e-02
	Necroptosis	-1.9332	91	9.1e-02
	Apoptosis	-1.9173	109	9.9e-02
	Viral carcinogenesis	-1.8962	124	1.0e-01
	Phagosome	-1.8782	77	8.7e-02

### Supplementary Table 3 KEGG Enrichment: A549 NADK VS. A549 Control

Direction	GSEA analysis: NA vs EV	NES	Genes	adj.Pval
	Alcoholic liver disease	-1.8758	91	9.1e-02
	T cell receptor signaling pathway	-1.8295	63	8.6e-02
	Transcriptional misregulation in cancer	-1.8214	117	1.0e-01
	PD-L1 expression and PD-1 checkpoint pathway in cancer	-1.8166	59	8.6e-02
	Toxoplasmosis	-1.7731	65	8.7e-02
	Yersinia infection	-1.7655	101	9.7e-02
	Proteasome	-1.7554	35	8.6e-02
	Glycerophospholipid metabolism	-1.7456	64	8.7e-02
	Acute myeloid leukemia	-1.7234	50	8.7e-02
Up	GABAergic synapse	1.878	36	3.4e-02
	Morphine addiction	1.8565	42	3.4e-02
	Gastric acid secretion	1.8313	38	4.0e-02
	Taste transduction	1.8016	16	6.0e-02
	Calcium signaling pathway	1.7919	105	1.3e-02
	Salivary secretion	1.7721	39	5.7e-02
	Olfactory transduction	1.7703	16	6.7e-02
	Bile secretion	1.7288	31	6.7e-02
	TGF-beta signaling pathway	1.7246	68	4.0e-02
	Dilated cardiomyopathy	1.7176	50	5.8e-02