

Table S1. RT-PCR primer sequences for mouse and human target genes used in this study.

Gene name	Primer direction	Primer sequences (5'-3')
Actin-mouse	Forward Primer	GTGACGTTGACATCCGTAAAGA
	Reverse Primer	GCCGGACTCATCGTACTCC
Collagen 1-mouse	Forward Primer	GCTCCTCTTAGGGGCCACT
	Reverse Primer	CCACGTCTCACCATTGGGG
Tgfb1-mouse	Forward Primer	CAATTCCTGGCGATACCTCAG
	Reverse Primer	GCACAACTCCGGTGACATCAA
E-cadherin-mouse	Forward Primer	CAGGTCTCCTCATGGCTTTGC
	Reverse Primer	CTTCCGAAAAGAAGGCTGTCC
Vimentin-mouse	Forward Primer	CGTCCACACGCACCTACAG
	Reverse Primer	GGGGGATGAGGAATAGAGGCT
GAPDH-human	Forward Primer	AATTCCATGGCACCCTCAAGG
	Reverse Primer	TGCAAATGAGCCCCAGCCT
Fibronectin-human	Forward Primer	AGGAAGCCGAGGTTTTAACTG
	Reverse Primer	AGGACGCTCATAAGTGTACC
ZO1-human	Forward Primer	CAACATACAGTGACGCTTCACA
	Reverse Primer	CACTATTGACGTTTCCCCACTC
SFN-human	Forward Primer	ACTTTTCCGTCTTCCACTACGA
	Reverse Primer	ACAGTGTCAGGTTGTCTCGC
PHPT1-human	Forward Primer	GCGGACCTCGCTCTCATTC
	Reverse Primer	CGCACGATCTCCTTGCTCT
PARD3-human	Forward Primer	GGGGACGGCCACATGAAAG
	Reverse Primer	TTCCAAGCGATGCACCTGTAT
NT5C-human	Forward Primer	ACCTGGCGGATAAAGTGGC
	Reverse Primer	GGTAGGTCGTTTCATCTCCCG

Table S2. Top 10 compounds with expression profiles similar to the epithelial–mesenchymal transition (EMT) model.

Name	Category	Function Description
Etoposide	Therapeutic drugs, chemotherapy drugs	Topoisomerase II inhibitor, blocking DNA replication and repair
Sunitinib	Therapeutic drugs, targeted drugs	Multi-target tyrosine kinase inhibitor (VEGFR/PDGFR/c-Kit), anti-angiogenesis, anti-tumor proliferation
Teniposide	Therapeutic drugs, chemotherapy drugs	Topoisomerase II inhibitor, blocking DNA replication and repair
Fdcyd	Therapeutic drugs, chemotherapy drugs	Antimetabolites, interfering with DNA/RNA synthesis
Idarubicin	Therapeutic drugs, chemotherapy drugs	Anthracycline antibiotics, intercalating into DNA and inhibiting topoisomerase II
3-Cl-AHPC	Tool compounds, research tool drugs	Alkylated phospholipid analogs, inducing tumor cell apoptosis and inhibiting proliferation
CD-437	Tool compounds, research tool drugs	Retinoic acid receptor (RAR) agonists, inducing differentiation and apoptosis
VLX-600	Tool compounds, research tool drugs	Histone deacetylase (HDAC) inhibitors, affecting epigenetics
Vincristine	Therapeutic drugs, chemotherapy drugs	Microtubule inhibitors, blocking mitosis
AMG-232	Tool compounds, clinical investigational drugs	MDM2 inhibitor, activating the p53 pathway

Table S3. Top 5 compounds with expression profiles inversely correlated to the epithelial–mesenchymal transition (EMT) model.

Name	Category	Function Description
Colforsin	Tool compounds, modeling tool drugs	Adenylyl cyclase activator, increasing cAMP
Triacsin-c	Tool compounds, modeling tool drugs	Lipid metabolism inhibitor, inhibiting long-chain acyl-CoA synthetase
Vemurafenib	Therapeutic drugs, targeted drugs	BRAF V600E inhibitor
Brefeldin-a	Tool compounds, modeling tool drugs	Protein transport inhibitor, blocking transport from the endoplasmic reticulum to the Golgi apparatus
Rapamycin	Therapeutic drugs, modeling tool drugs	mTOR inhibitor

Note: BRD-K series identifiers (e.g., BRD-K66618978, BRD-K73059376, etc.) are unique catalog numbers used in the compound library of the Broad Institute (Broad Institute of MIT and Harvard).

These compounds may have known or unknown biological activities; however, their specific targets, mechanisms of action, or chemical structures cannot be determined by the identifier alone.

A

CCK8

ns **** ****

Cell viability

24 h 48 h 72 h

Fibronectin

** **** ****

24 h 48 h 72 h

ZO1

**** ** *

24 h 48 h 72 h

Control
BLM 2.5 μ M
BLM 5.0 μ M

B

Control RAPA BLM BLM+RAPA Control RAPA BLM BLM+RAPA

Hoechst

Vimentin

Merge

24 h 48 h

5 μ m

C

Control RAPA BLM BLM+RAPA Control RAPA BLM BLM+RAPA

24 h 48 h

Relative Level

24 h_Vimentin

48 h_Vimentin

Relative Level

24 h_α-SMA

48 h_α-SMA

Relative Level

Control RAPA BLM BLM+RAPA

(A) Cell viability of A549 cells exposed to gradient concentrations of BLM. Analyzed via two-way ANOVA (n = 3).

(C) Immunofluorescence staining for vimentin (green) in A549 cells at 24 h and 48 h after BLM treatment; nuclei counterstained with Hoechst (blue). 200× magnification (cropped view), scale bar = 5 μm. Fluorescence intensity analyzed via one-way ANOVA (n = 3).

(D) Immunofluorescence staining for α -SMA (red) in A549 cells at 24 h and 48 h after BLM treatment; nuclei counterstained with Hoechst (blue). 200 $\times$ magnification (cropped view), scale bar = 5 μ m. Fluorescence intensity analyzed via one-way ANOVA (n = 3).

Data are shown as mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. All statistical tests were two-sided.

Figure S2

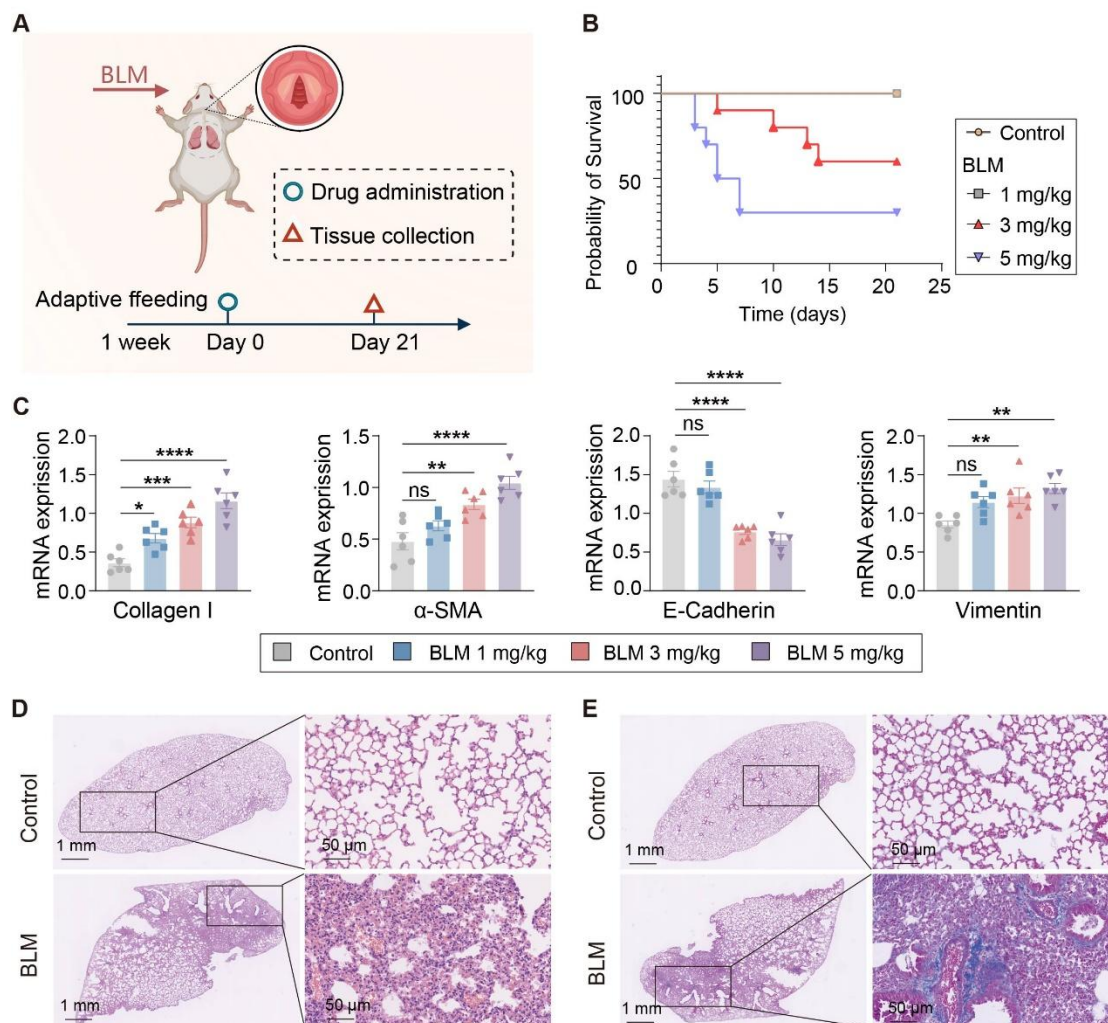


Figure S2. Bleomycin induces pulmonary fibrosis in mice.

(A) Schematic illustration of BLM-induced pulmonary fibrosis mouse model establishment.

(B) Kaplan–Meier survival curves of mice administered with escalating intratracheal BLM doses. Analyzed by log-rank test (n = 10).

(C) Relative mRNA levels of *Colla1*, *Acta2*, *Cdh1*, and *Vim* in mouse lung tissues. Analyzed via one-way ANOVA (n = 6).

(D and E) Representative H&E (D) and Masson's trichrome (E) staining of lung sections from control and 3 mg/kg BLM-treated mice. Images captured at 20× (scale bar = 100 μm) or 400× (scale bar = 50 μm), as indicated on each panel (n = 6).

Data are shown as mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. All statistical tests were two-sided.

A

B

C

D

E

F

G

Figure S3. Multi-omics profiling and clinical pathway enrichment in BLM-induced pulmonary fibrosis.

(A) Heatmap of differentially expressed genes (DEGs) from transcriptomic analysis of mouse lung tissues.

(B) Venn diagram showing overlapping DEGs among the control, BLM, and BLM+RAPA mouse groups.

(C) Volcano plots of differentially expressed proteins (DEPs) from proteomic analysis of mouse lung tissues.

(D) Protein–protein interaction (PPI) network of differentially expressed genes between BLM+RAPA and BLM groups from multi-omics data.

(E) KEGG pathway enrichment analysis of DEGs derived from transcriptomic profiling of mouse lung tissues.

(F) GO functional enrichment analysis of proteomic data from mouse lung tissues.

(G) KEGG and GO pathway enrichment analyses based on the human IPF dataset GSE53845.

Data are shown as mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. All statistical tests were two-sided.

Figure S4

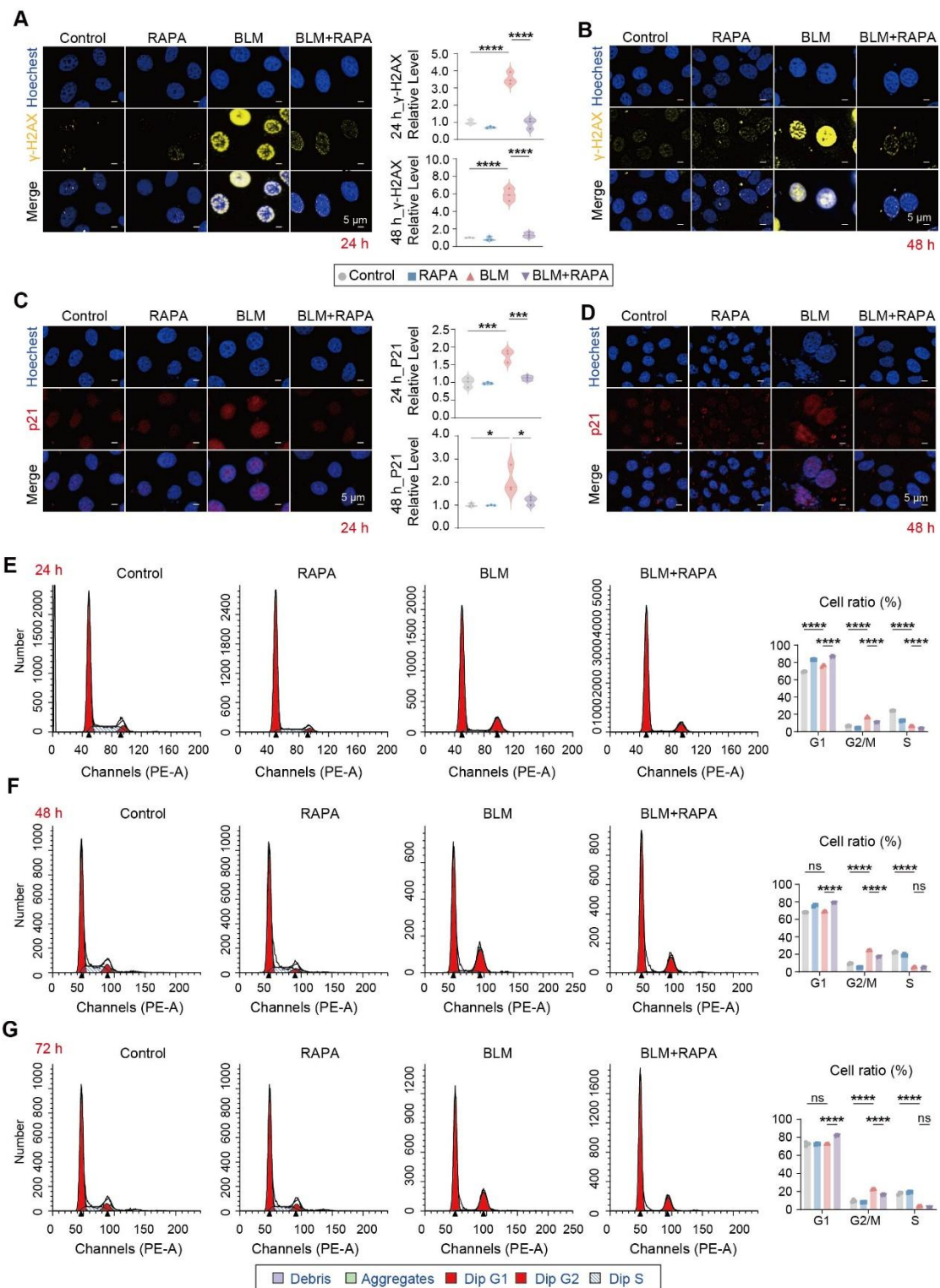


Figure S4. Rapamycin alleviates BLM-induced DNA damage and cellular senescence.

(A and B) Immunofluorescence staining for γ H2AX (yellow) in A549 cells at 24 h and 48 h post-treatment; nuclei counterstained with Hoechst (blue). 200 $\times$ magnification (cropped view), scale bar = 5 μ m. Fluorescence intensity analyzed via one-way ANOVA (n = 3).

(C and D) Immunofluorescence staining for p21 (red) in A549 cells at 24 h and 48 h post-treatment; nuclei counterstained with Hoechst (blue). 200 $\times$ magnification (cropped view), scale bar = 5 μ m. Fluorescence intensity analyzed via one-way ANOVA (n = 3).

(E, F, and G) Cell cycle distribution of A549 cells treated with BLM alone or combined with RAPA for 24, 48, and 72 h, determined by flow cytometry. Bar graphs show the quantitative percentages of cells in G1, S, and G2/M phases. Data analyzed via two-way ANOVA (n = 3).

Data are shown as mean $\pm$ SEM. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. All statistical tests were two-sided.

Figure S5

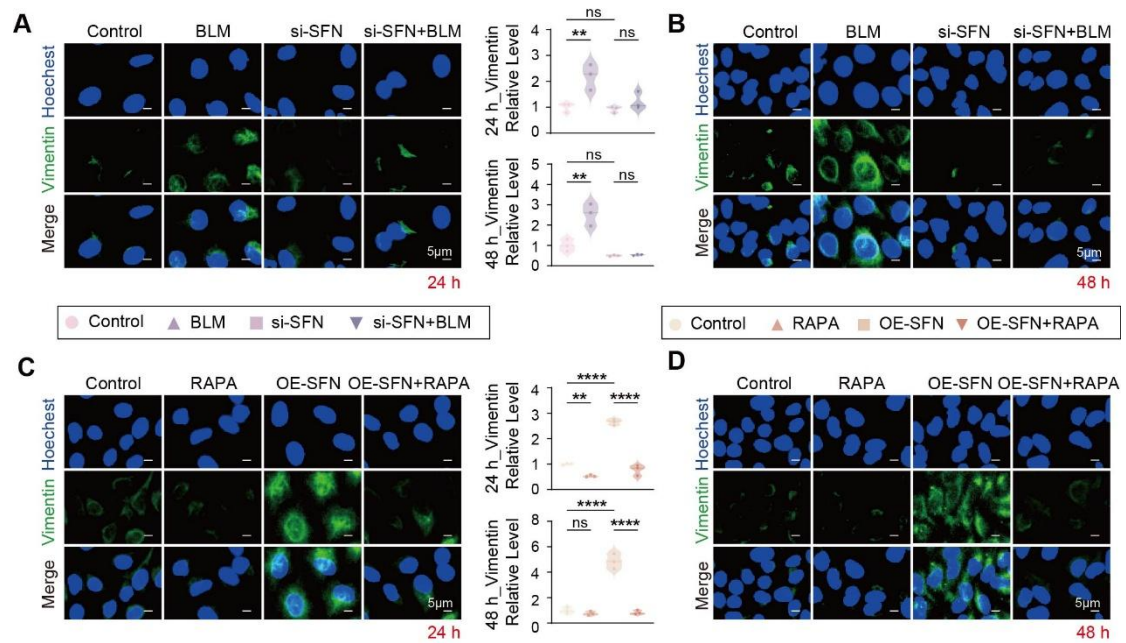


Figure S5. SFN mediates BLM-induced EMT in A549 alveolar epithelial cells. Related to Figure 4.

(A and B) Immunofluorescence staining for vimentin (green) in *SFN*-knockdown A549 cells at 24 h and 48 h post-treatment; nuclei counterstained with Hoechst (blue). 200× magnification (cropped view), scale bar = 5 μm. Fluorescence intensity quantified via one-way ANOVA (n = 3).

(C and D) Immunofluorescence staining for vimentin (green) in *SFN*-overexpressing A549 cells at 24 h and 48 h post-treatment; nuclei counterstained with Hoechst (blue). 200× magnification (cropped view), scale bar = 5 μm. Fluorescence intensity quantified via two-way ANOVA (n = 3).

Data are shown as mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. All statistical tests were two-sided.