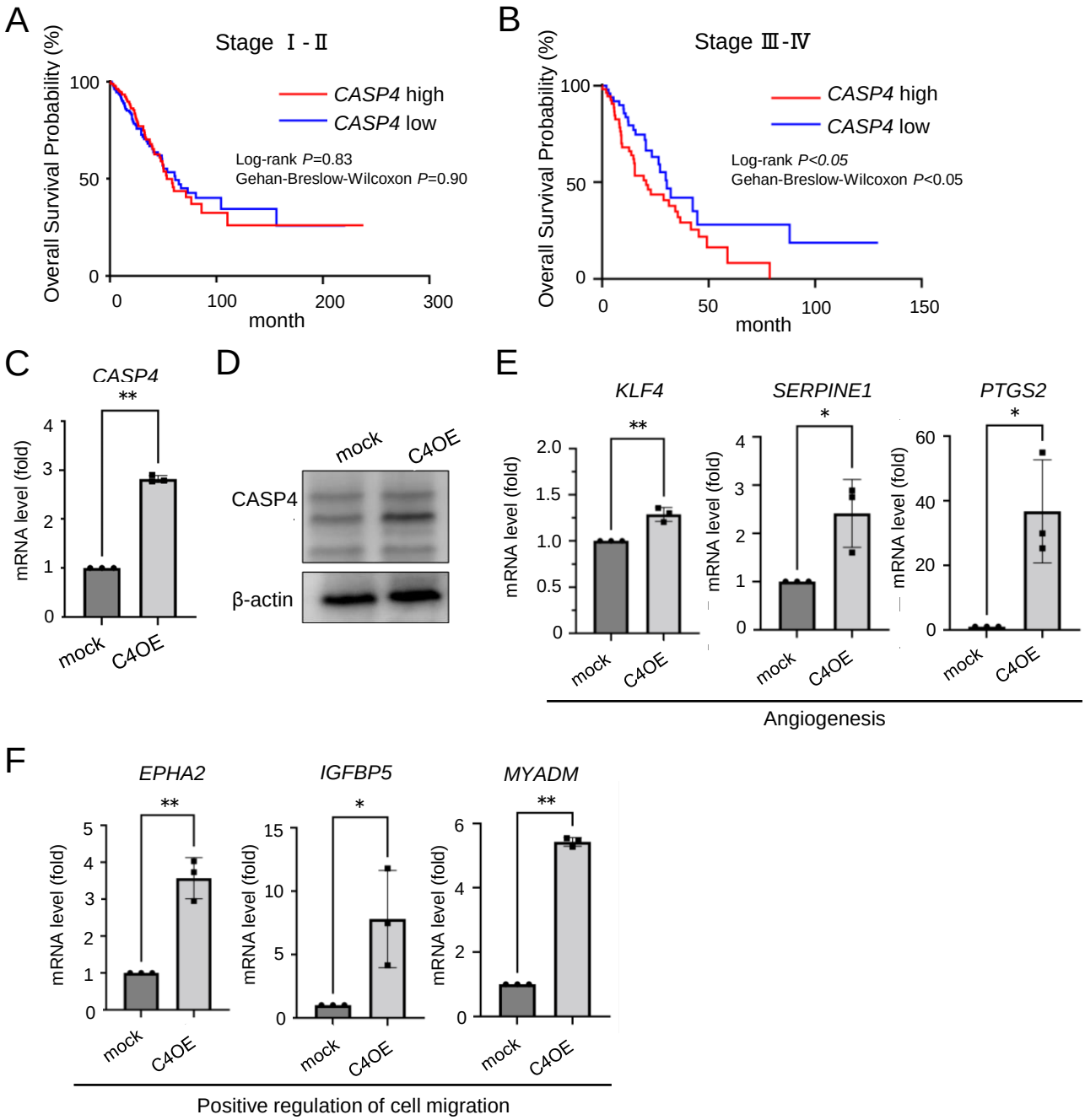


**Figure S1. CASP4 overexpression upregulates cell migration, angiogenesis, and related genes in A549 cells (Related to Figure 1).**

(A) and (B) Comparison of overall survival by *CASP4* mRNA expression based on The Cancer Genome Atlas Program (TCGA) and Lung Adenocarcinoma (LUAD) database analysis (stage Ⅰ–Ⅱ: n = 399, stage Ⅲ–Ⅳ: n = 110); *CASP4* high is defined as mRNA expression z-scores relative to all samples (log RNA-Seq V2 RSEM) of >0.08, and *CASP4* low is defined below that. (C) Comparison of *CASP4* mRNA expression between mock and *CASP4* overexpressing (C4OE) cells by real-time quantitative PCR (RT-qPCR). (D) Representative images of the immunoblotting analysis of CASP4 protein levels in mock and C4OE cells. (E) and (F) Representative angiogenesis and cell motility-related genes upregulated by C4OE by RT-qPCR. *P < 0.05, **P < 0.01 compared with mock.

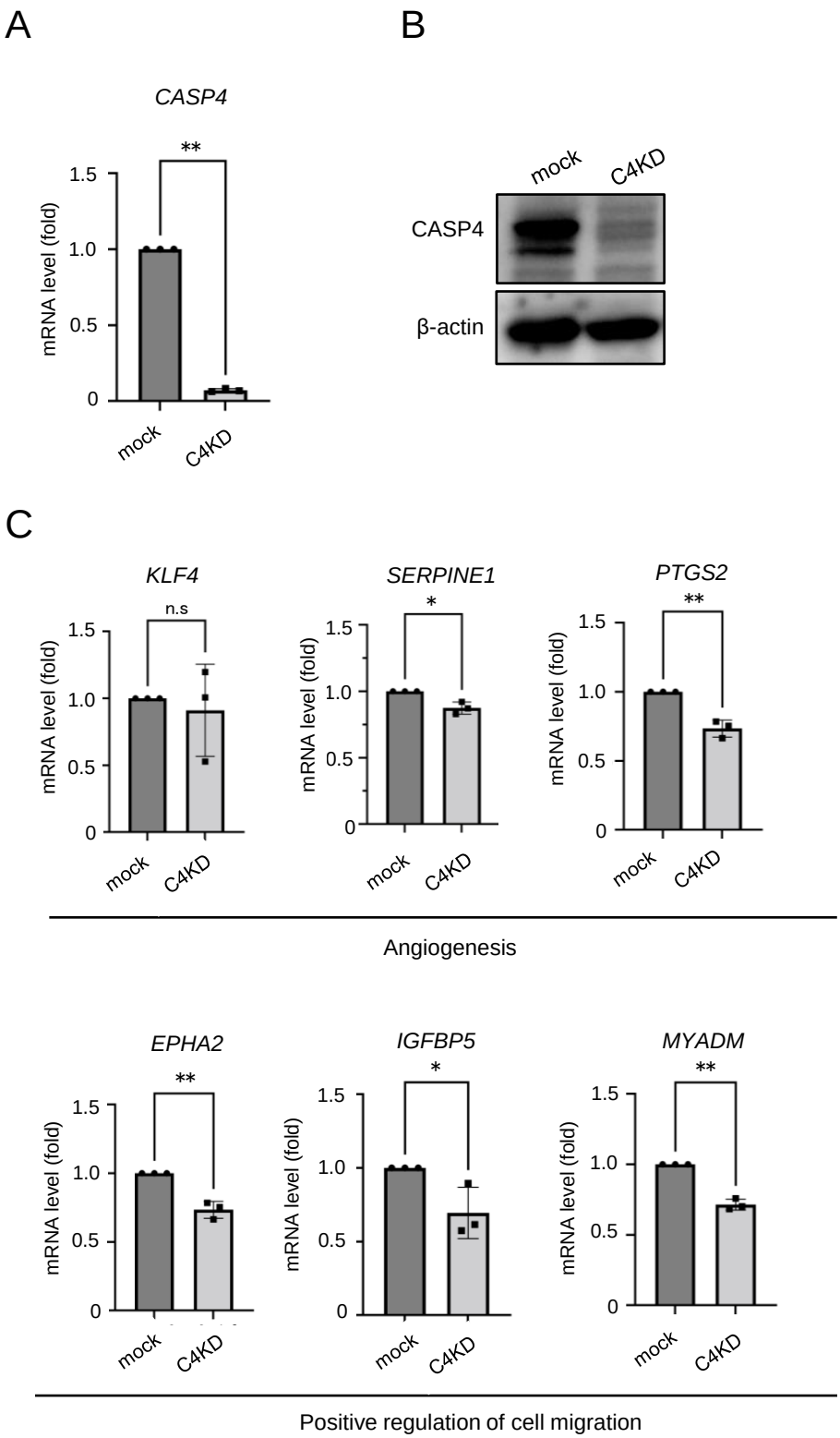


**Figure S2. CASP4 knockdown decreases angiogenesis and cell motility-related genes in H1975 cells (Related to Figure 2).**

(A) Comparison of CASP4 mRNA expression between mock and CASP4 knockdown (C4KD) cells by RT-qPCR. (B) Representative images of the immunoblotting analysis of CASP4 protein levels in mock and C4KD cells. (C) Representative angiogenesis and cell motility-related genes downregulated by CASP4 knockdown by RT-qPCR. n.s.: not significant, *P < 0.05, **P < 0.01 compared with mock.

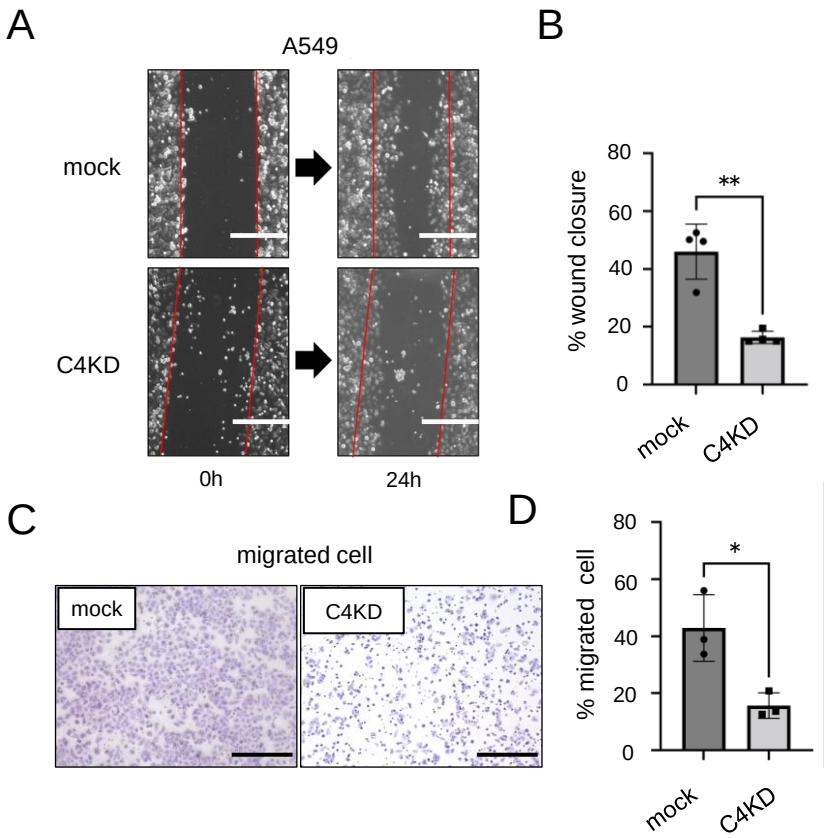


**Figure S3. CASP4 promotes cell migration in A549 cells (Related to Figure 3).**

(A) Representative images of the wound healing assay of mock or C4KD A549 cells at 0 and 24 h. Scale bar, 500 µm. (B) Quantitative analysis of cell motility in A by mock or C4KD A549 cells as indicated by the rate of % wound closure of a scratched area at 24 h (n = 3). (C) Representative images of cell migration assay of mock or C4KD A549 cells at 48 h. Scale bar, 100 µm. (D) Quantitative analysis of cell migration in E by mock or C4KD A549 cells as indicated by the rate of % migrated cell at 48 h(n = 3). *P < 0.05, **P < 0.01 compared with the mock.

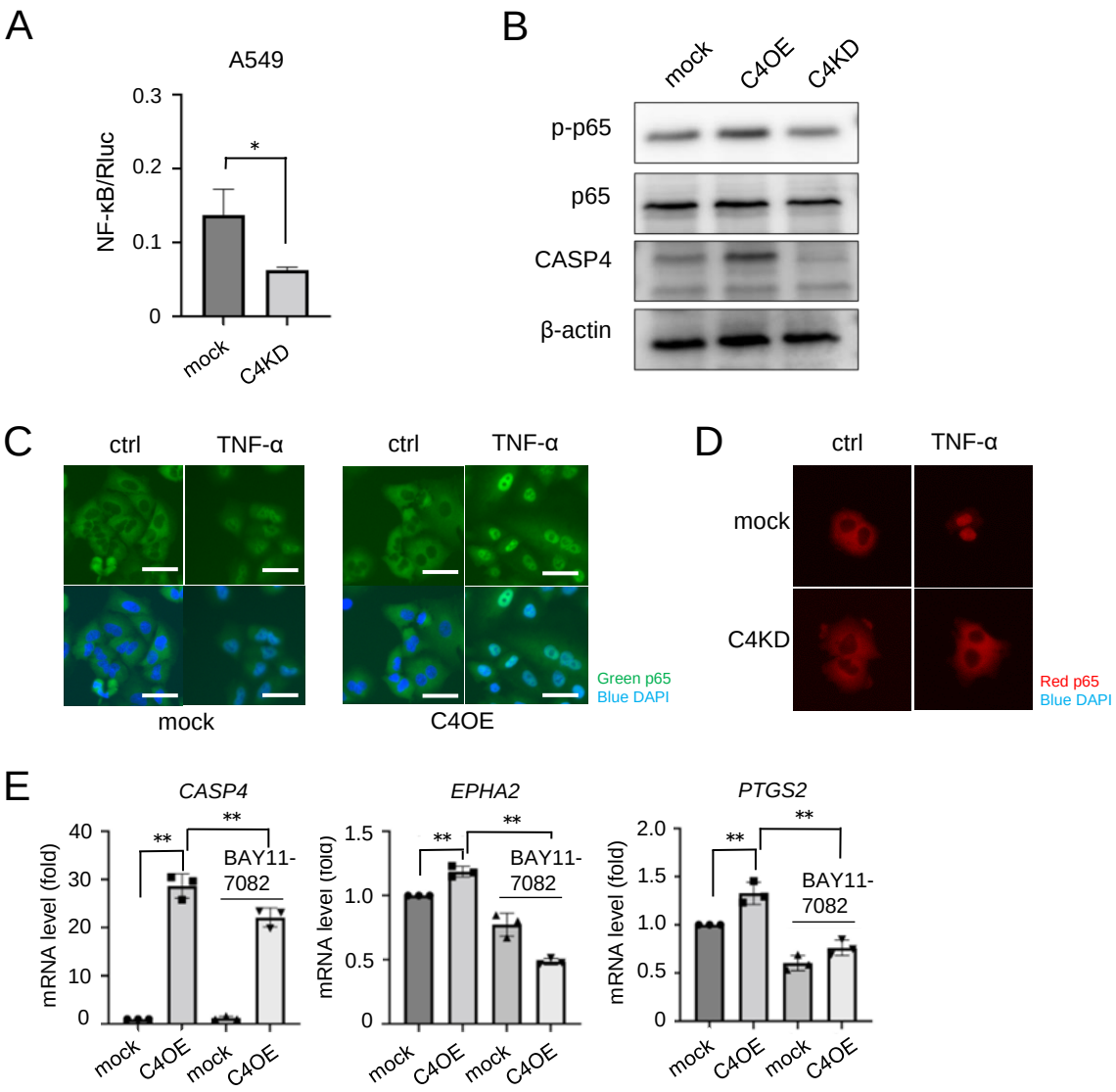


**Figure S4. CASP4 activates NF-κB in A549 cells (Related to Figure 5).**

(A) Relative comparison of luciferase activity between mock and C4KD A549 cells transfected with an NF-κB expression plasmid. (B) Immunoblotting analysis of phospho-p65, p65, and CASP4 protein levels in mock and C4KD A549 cells. (C)(D) Expression and localization of p65 by immunofluorescence staining in mock and C4OE or C4KD A549 cells treated with 20 ng/ml of TNF-α for 1 h. Scale bar, 20 μm. (E) mRNA levels of CASP4, EPHA2, and PTGS2 in mock, and C4OE with or without the treatment of NF-κB inhibitor BAY11-7082 (10 μM) in A549 cells by RT-qPCR. *P < 0.05, **P < 0.01 compared with mock.

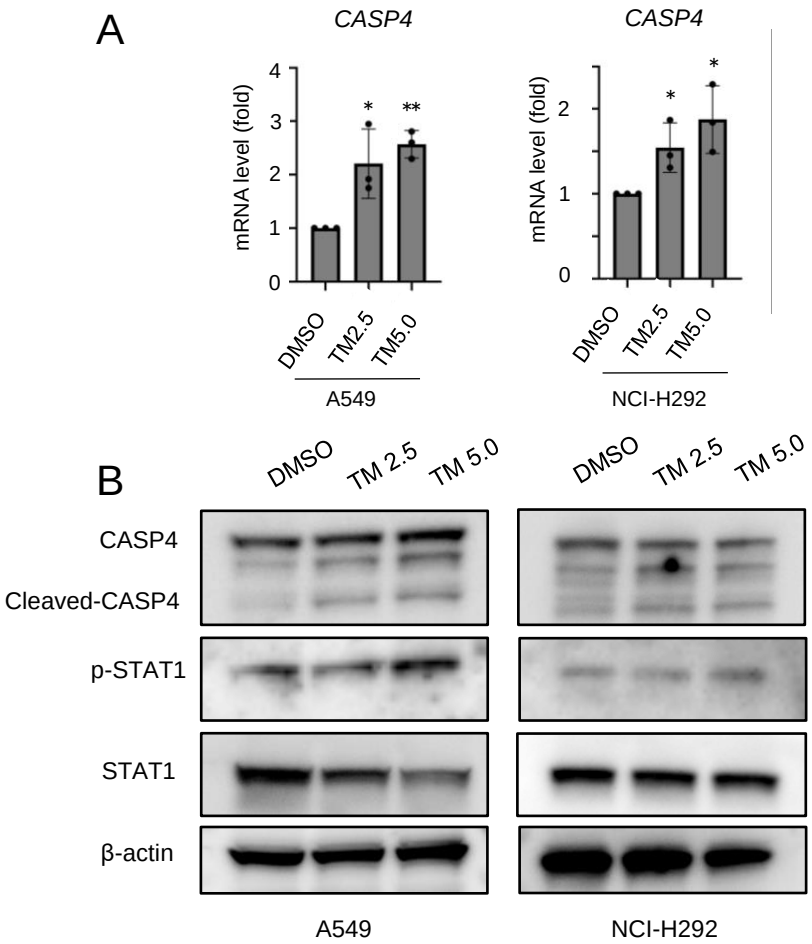


**Figure S5. CASP4 is induced by ER stress (Related to Figure 6).**

(A) Induction of CASP4 mRNA by the ER stress inducer tunicamycin (TM, μg/ml) by RT-qPCR. (B) Immunoblotting analysis of CASP4 and STAT1 treated with PBS and TM (μg/ml) in A549 and NCI-H292 cells. *P < 0.05, **P < 0.01 compared with mock.

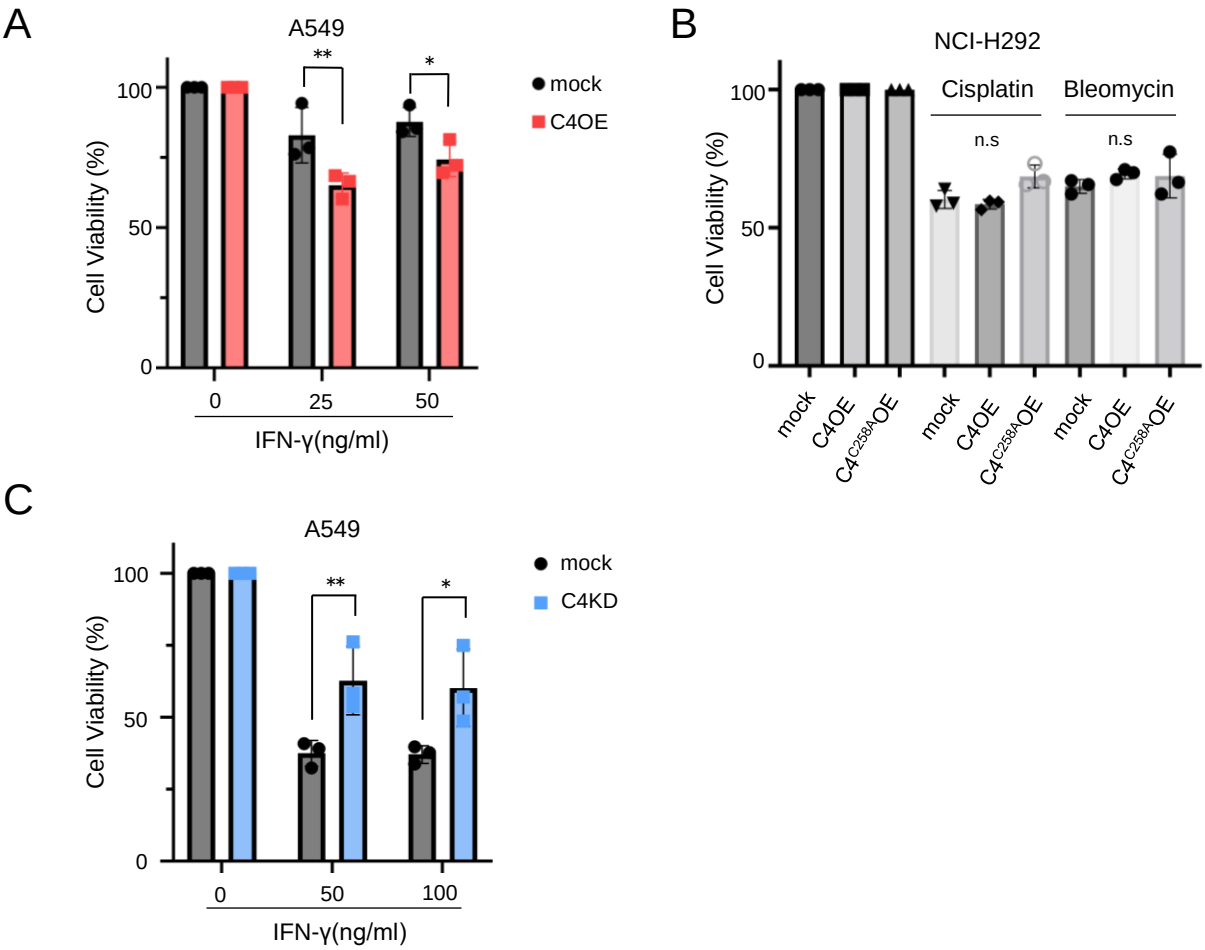


**Figure S6. CASP4 expression in NSCLC increases the susceptibility of IFN-γ to induce cell death (Related to Figure 7).**

(A) The rate of viable cells of mock, C4OE A549 cells treated with 100 ng/ml of IFN-γ measured by CCK-8 assay. (B) The rate of viable cells of mock, C4OE, and $C4^{C258A}OE$ NCI-H292 cells by cytotoxic reagents (cisplatin at 10 μM, and bleomycin at 50 μg/ml stimulated for 24 h) using CCK-8 assay. (C) The rate of viable cells of mock, CASP4 knockdown (C4KD) A549 cells treated with 50 or 100 ng/ml of IFN-γ measured by CCK-8 assay. n.s.: not significant, *P < 0.05, **P < 0.01 compared with mock.