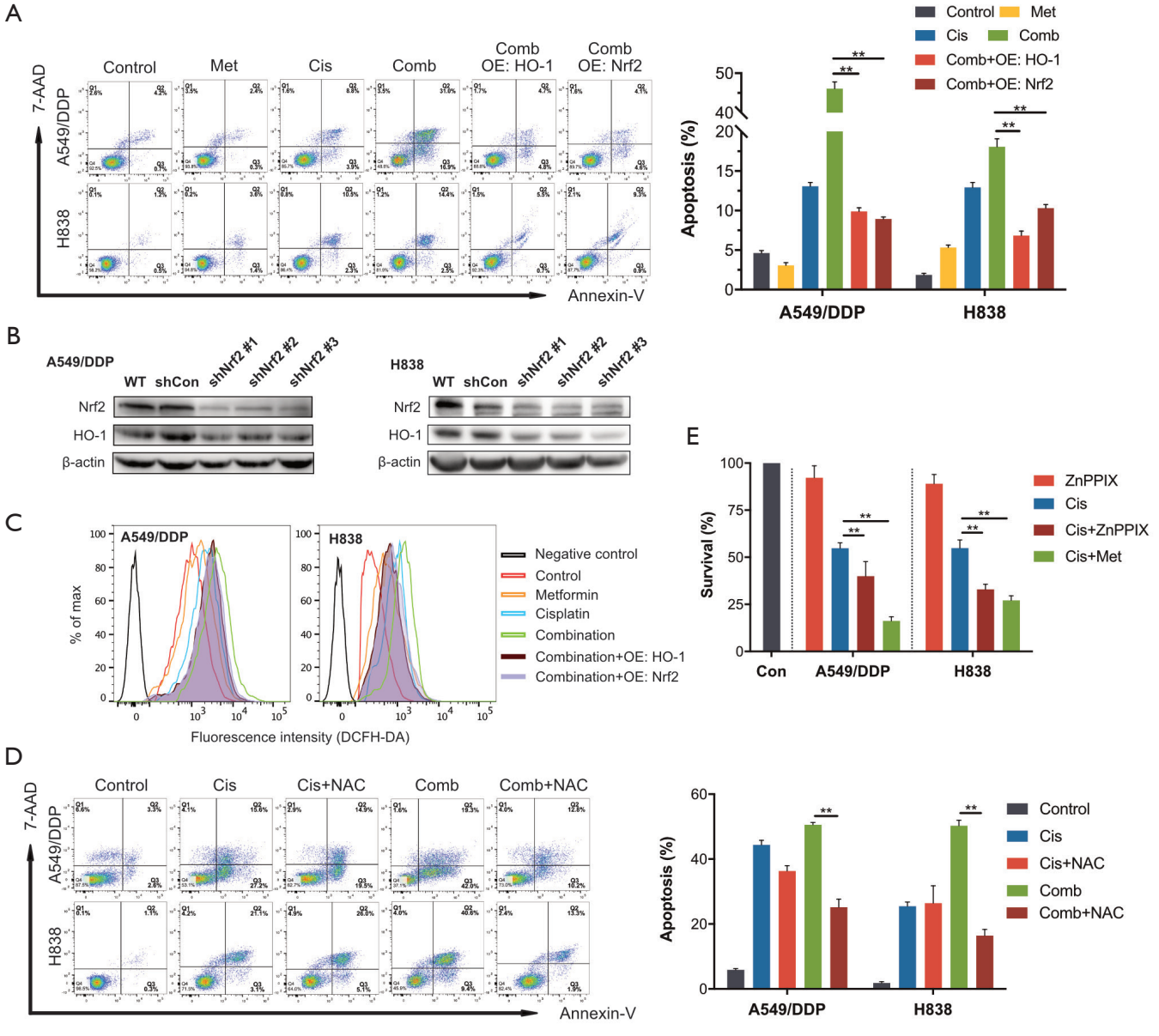

Figure S1 Metformin reverses cisplatin resistance in NSCLC cells via weakening Nrf2-mediated capacity for ROS detoxification. (A) Overexpression of Nrf2 and HO-1 blocked the synergistic effects on cellular apoptosis. NSCLC cells (A549/DDP and H838) were treated with metformin (3.2 and 12.8 mM, respectively) and/or cisplatin (32 and 2 μM, respectively) for 48 h after overexpression of HO-1 or Nrf2 for 48 h. NSCLC cells were examined using Annexin-V/7-AAD staining, and the distribution of apoptotic cells was measured by flow cytometry analysis. (B) NSCLC cells were transfected with lentivirus containing an shRNA sequence (shNrf2 #1, #2 and #3) targeting Nrf2 or control shRNA, and selected with puromycin. Western blot analysis of the levels of Nrf2/HO-1 axis in NSCLC cells after stable knockdown. (C) NSCLC cells were stained with DCFH-DA, an oxidation-sensitive fluorescent probe (the negative control was not treated with DCFH-DA). Flow cytometry showing decreased ROS accumulation in HO-1- and Nrf2-overexpressing NSCLC cells after combination therapy. (D) ROS scavenger NAC blocked the synergistic inhibitory effects on cell death. NSCLC cells (A549/DDP and H838) were treated with metformin (3.2 and 12.8 mM, respectively), cisplatin (40 and 6 μM, respectively) and NAC (100 μM) in combination or each alone for 48 h. NSCLC cells were examined using Annexin-V/7-AAD staining, and the distribution of apoptotic cells was measured by flow cytometry analysis. (E) The effects of metformin and ZnPPIX (10 μM), a specific HO-1 inhibitor, on the NSCLC cell proliferation were assessed by CCK-8 assay. All experiments were independently repeated at least three times. Bars represent the means ± SDs. **, P<0.001, by one-way analysis of variance followed by Tukey's multiple comparisons test. NSCLC, non-small cell lung cancer; Cis, cisplatin; Met, metformin; Comb, combination; Con, control; WT, wild-type; OE, overexpression; NAC, N-acetyl cysteine.

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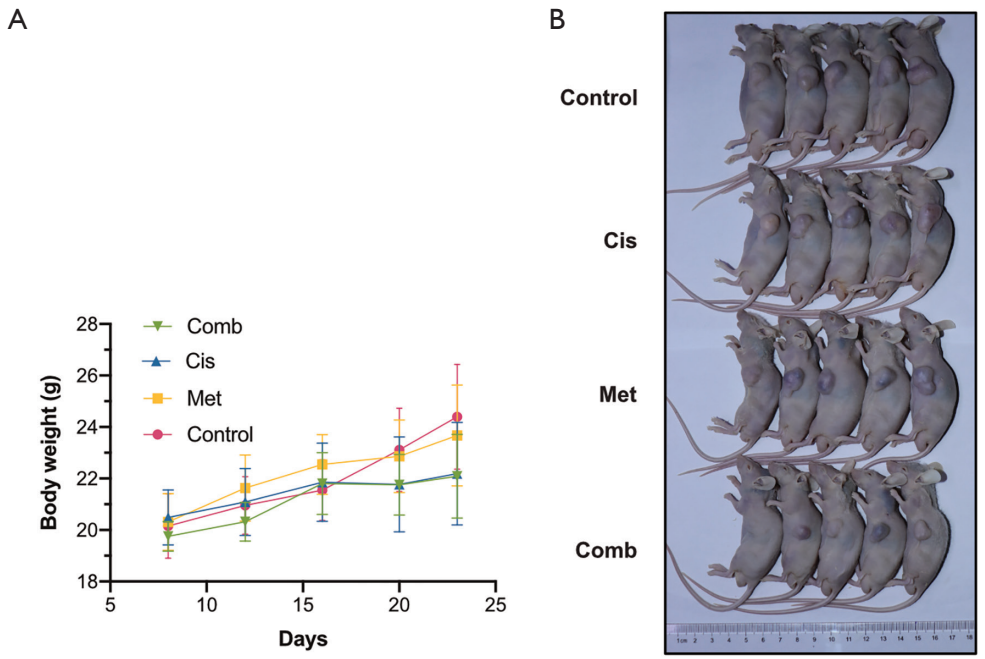

Figure S2 Evaluation of drug toxicity in xenograft models. (A) Mice weights during *in vivo* treatments. Weight referring to treatments with cisplatin (2 mg/kg; qod) and metformin (200 mg/kg; qd) in combination or alone. (B) Image of xenograft models on day 23. Points, error bars and connecting lines on the graph indicate the means and error ± SDs. Cis, cisplatin; Met, metformin; Comb, combination.

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Table S1 Comparison of patient characteristics for different clinical response to platinum-containing chemotherapy

Characteristics	SD (n=14)	PR (n=36)	OR (95% CI)	P value
Age			–	0.39
Mean (Std. Dev)	59.86 (8.28)	61.75 (6.34)		
Sex			1.18 (0.16 to 16.42)	>0.99
Male	13	33		
Female	1	3		
Smoking (pack/year)				0.53
≥30	11	29	1.00 (reference)	
0–30	2	2	2.64 (0.33 to 21.09)	0.36
0	1	5	0.53 (0.06 to 5.04)	0.58
Weight loss			–	0.30
Yes	0	5		
No	14	31		
Stage after surgery				0.77
I	0	2	–	0.99
IIa	1	1	3.50 (0.18 to 69.34)	0.41
IIb	4	14	1.00 (reference)	–
IIIa	4	12	1.17 (0.24 to 5.70)	0.85
IIIb	5	7	2.50 (0.51 to 12.35)	0.26
Tumor size			–	0.08
Mean (SD)	3.64 (1.82)	2.67 (1.66)		
Histology				0.98
Adenocarcinoma	1	3	0.80 (0.08 to 8.37)	0.85
Squamous	13	31	1.00 (reference)	–
Other	0	2	–	>0.99
Grade			–	0.93
G1	1	0	–	>0.99
G2	4	14	0.64 (0.16 to 2.48)	0.51
G3	9	20	1.00 (reference)	–
Missing	0	2	–	>0.99
Tumor location			0.50 (0.13 to 1.85)	0.44
Central	10	30		
Peripheral	4	6		
First-line treatment				0.88
doc/cis (DP)	4	11	0.68 (0.16 to 2.93)	0.6
gem/cis (GP)	7	13	1.00 (reference)	–
pem/carbo (PC)	1	7	0.27 (0.03 to 2.61)	0.26
pem/cis (PP)	1	3	0.62 (0.05 to 7.12)	0.70
tax/carbo (TC)	0	1	–	>0.99
tax/cis (TP)	1	1	1.86 (0.10 to 34.44)	0.68

n, Number of patients; CI, confidence interval; OR, odds ratio; Std. Dev, standard deviation; SD, stable disease; PR, partial response; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; doc, docetaxel; cis, cisplatin; gem, gemcitabine; pem, pemetrexed; carbo, carboplatin; tax, paclitaxel.

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