Figure S1. Oxaliplatin promotes XPO1 expression. (A) Immunoblot analysis of HCT116/L-OHP, HCT116, HCT8/L-OHP and HCT8 cells. (B) Immunoblot analysis of HCT116 and HCT8 cells treated with oxaliplatin (0, 1, 2, 4, 8 or 16 μM) for 48 h. XPO1, exportin 1.

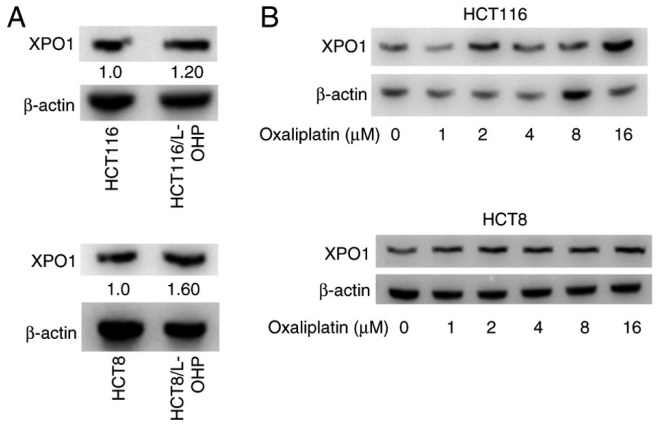

Figure S2. Cell cycle analysis of CRC cells following treatment. (A) Cell cycle analysis by flow cytometry after treatment with oxaliplatin (2 μM) for 48 h. (B) Cell cycle distribution detected by flow cytometry after 48 h of treatment with oxaliplatin (10 μM), KPT-330 (33 nM) or the combination.

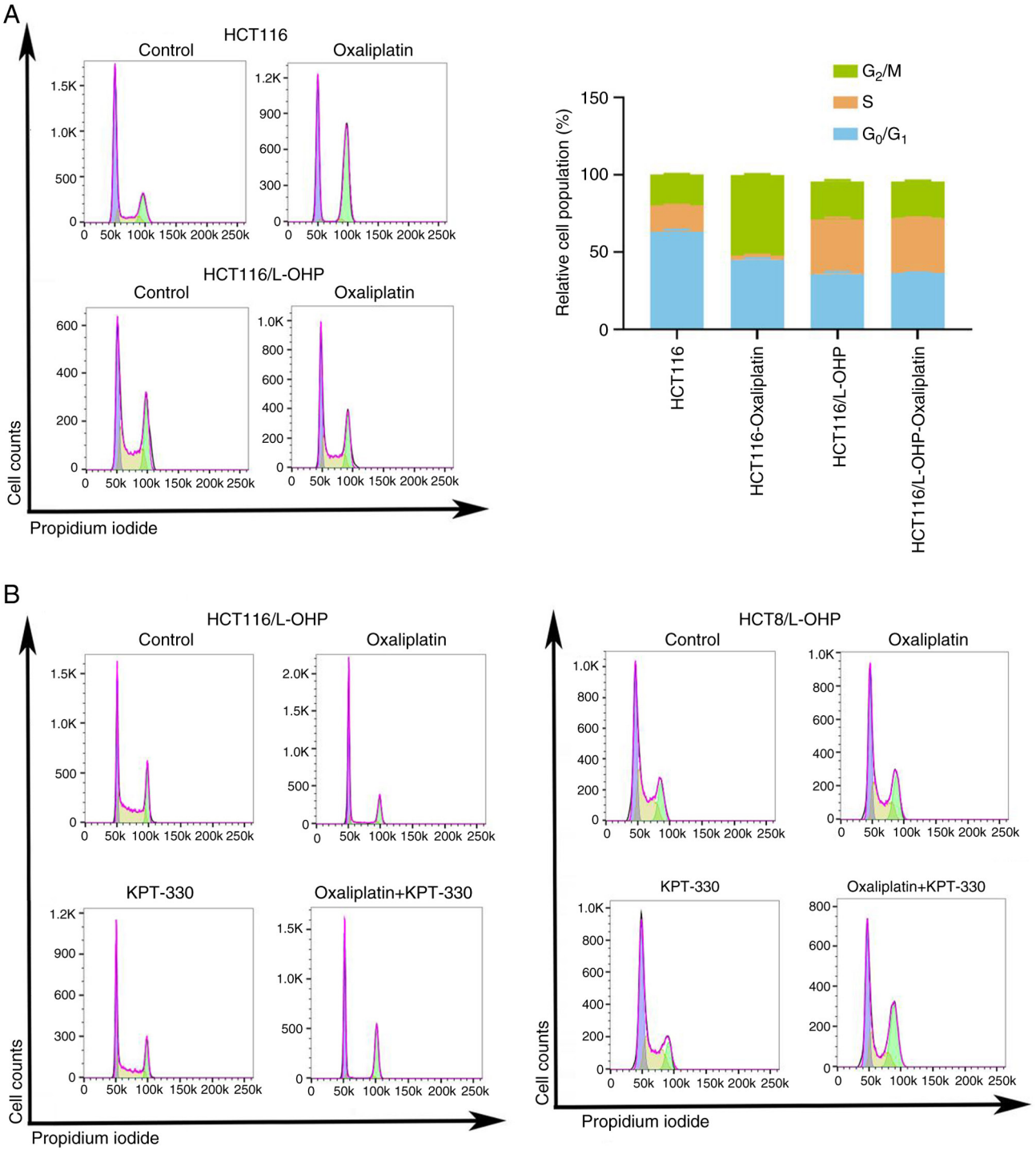

Figure S3. Effects of oxaliplatin on oxaliplatin-sensitive or resistant cells. (A) Apoptosis rate of HCT116/L-OHP and HCT116 cells treated with oxaliplatin (2 μM) for 48 h, assessed by flow cytometry. The sum of early apoptotic cells (annexin V^+/PI^-) in the lower-right quadrant and late apoptotic cells (annexin V^+/PI^+) in the upper-right quadrant indicates apoptotic cells, and was used for the quantification of cell death. (B) MMP in HCT116/L-OHP and HCT116 cells after 48 h of oxaliplatin (2 μM) treatment, analyzed by JC-1 staining and flow cytometry. The bar chart shows the relative MMP loss in the four groups. (C) Reactive oxygen species levels in HCT116/L-OHP and HCT116 cells after 48 h of oxaliplatin (2 μM) treatment, measured by DCFH-DA staining and flow cytometry. (D) Representative transmission electron microscopy images showing mitochondrial morphology in HCT116/L-OHP and HCT116 cells after 48 h of oxaliplatin (2 μM) treatment. Scale bars, 2 μm. ****P<0.0001. DCFH-DA, 2',7'-dichlorodihydrofluorescein diacetate; MMP, mitochondrial membrane potential; NS, not significant.

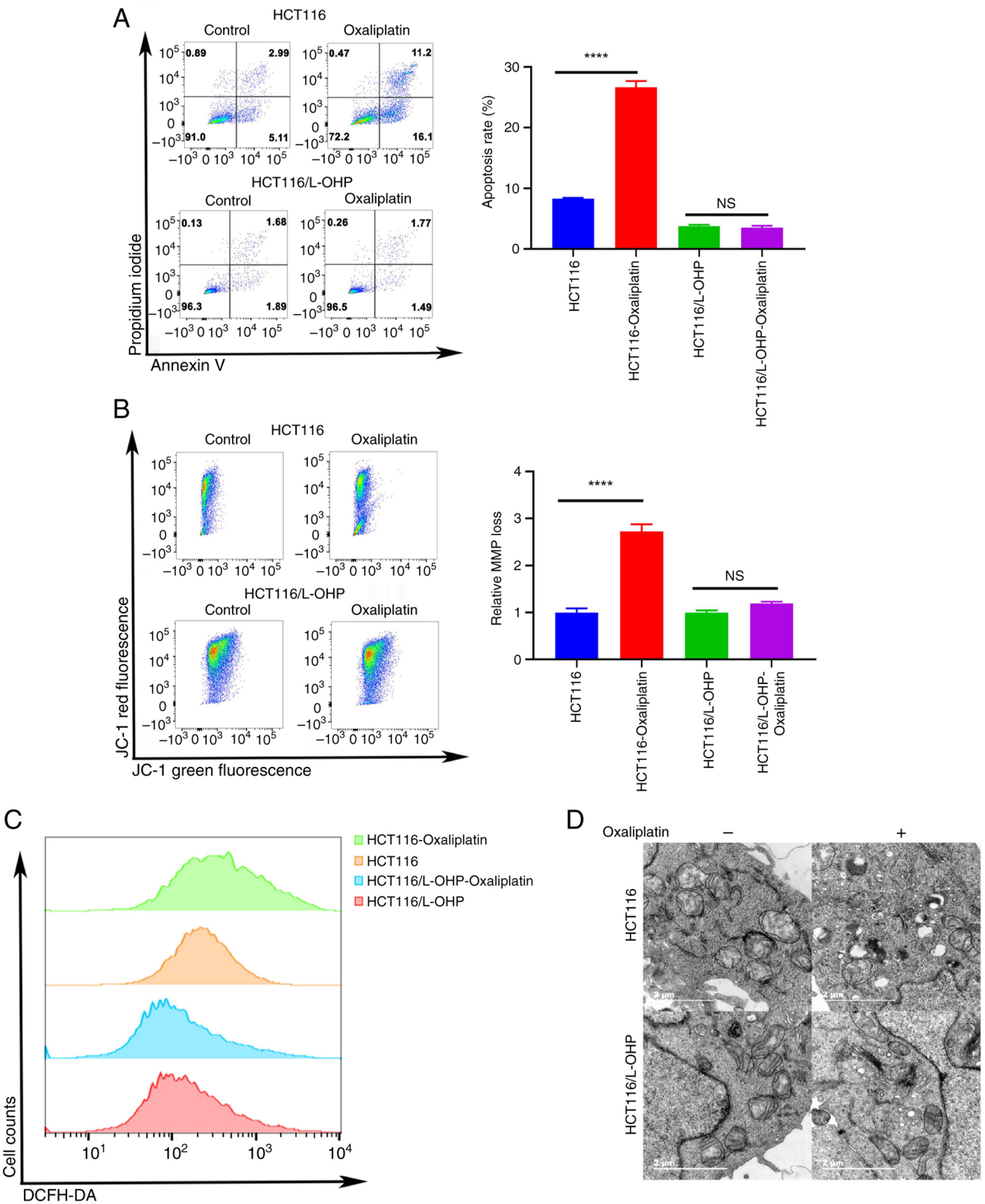

Figure S4. Knockdown efficiency of the p53 siRNA. Immunoblot analysis of HCT116/L-OHP cells after silencing of p53 or transfection with si-NC. NC, negative control; siRNA/si, small interfering RNA.

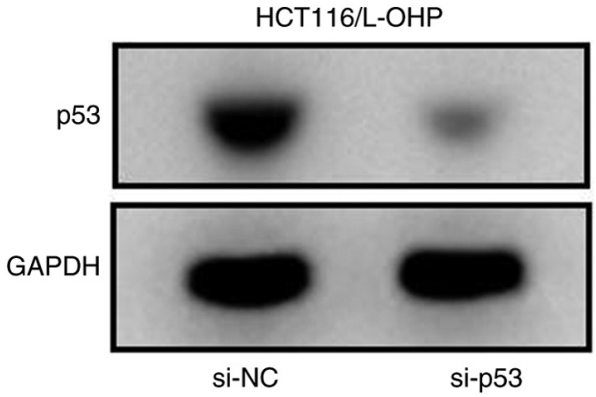

Figure S5. Pathway diagram illustrating how KPT-330 and oxaliplatin synergistically overcome oxaliplatin resistance in colorectal cancer. Oxaliplatin treatment alone increased XPO1 protein levels, which in turn facilitated the active shuttling of p53 from the nucleus to the cytoplasm. This resulting cytoplasmic mislocalization of p53 is closely associated with chemoresistance. Conversely, combination therapy with oxaliplatin and the XPO1 inhibitor KPT-330 blocked the XPO1-mediated nuclear export of p53, thereby promoting its accumulation within the nucleus. This crucial event subsequently led to p21 upregulation and SLC7A11 downregulation, which collectively induced mitochondrial dysfunction, and consequently enhanced apoptosis and ferroptosis. MMP, mitochondrial membrane potential; SLC7A11, solute carrier family 7 member 11; XPO1, exportin 1.