

RESEARCH ARTICLE

Cisplatin-Doped Black Phosphorus Nanomedicines Overcome Platinum-Based Anticancer Drug Resistance via Piezoelectric-Mediated Adaptive Homeostasis Disruption

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ABSTRACT

The clinical efficacy of platinum-based chemotherapeutics is frequently diminished by the emergence of resistance during prolonged treatment. Cisplatin (DDP)-resistant tumors adapt to chemotherapeutic stress by establishing a new state of adaptive homeostasis that sustains cellular survival under drug pressure, albeit at the expense of high metabolic burden and acquired vulnerability. Exploiting this intrinsic weakness, we designed a DDP-doped black phosphorus (BP) nanomedicine protected by polydopamine coating (DDP-BP@PDA) that synergistically delivered DDP and piezoelectric BP to precisely disrupt resistance homeostasis and thereby reverse DDP resistance. DDP-BP@PDA altered the intracellular uptake pathway of DDP and disrupted the redox balance of resistant cells via piezocatalysis. Concurrently, piezoelectric polarization enhanced the peroxidase-like activity via electron injection, leading to the generation of substantial reactive oxygen species (ROS). This ROS burst compromised the integrity of the endoplasmic reticulum (ER) membrane and exacerbated the protein-folding burden, thereby amplifying ER stress. Mechanism study reveals that excessive ER stress downregulated the expression of DNA repair proteins, making resistant cells highly sensitive to DDP-induced DNA damage. Through these synergistic effects, DDP-BP@PDA disrupted the adaptive homeostasis of DDP-resistant cells, thereby significantly inhibiting the progression of DDP-resistant tumors. This study establishes a promising therapeutic strategy to combat DDP-resistance via piezoelectric-driven disruption of adaptive homeostasis.

1 | Introduction

Platinum-based anticancer drugs, as broad-spectrum chemotherapeutics, have provided substantial clinical benefits in the treatment of diverse malignancies. However, prolonged treatment

frequently results in tumor relapse and the emergence of acquired resistance [1]. To withstand the cytotoxic pressure of platinum-based agents, tumor cells exploit their phenotypic plasticity [2], establishing a dynamic, multidimensional adaptive homeostasis through coordinated reprogramming at the metabolic, signaling,

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and epigenetic levels [3–5]. This adaptive state is sustained by the coordinated regulation of core defense mechanisms, such as drug uptake and transport, redox balance, and DNA repair [6]. Under sustained platinum stress, tumor cells remodel drug transport networks to reestablish a new influx-efflux equilibrium, thereby reducing intracellular drug accumulation and reinforcing resistance. Concurrently, platinum-resistant cells fortify their detoxification and antioxidant defenses, forming a redefined redox homeostasis that mitigates DDP-induced ROS generation and oxidative injury [7]. Most critically, persistent activation of the nucleotide excision repair (NER) pathway sustains a dynamic balance between DNA damage and repair, enabling cells to evade apoptosis [8, 9]. Therefore, targeted regulation of this adaptive homeostasis offers a promising therapeutic strategy for overcoming chemoresistance and eradicating resistant tumors.

The maintenance of this adaptive equilibrium depends on continuous energy supply, robust antioxidant systems, and hyper-activated DNA repair machinery, which collectively impose a persistent high load on the cellular metabolic and stress networks [10]. To meet these demands, some resistant cells activate non-specific uptake pathways such as macropinocytosis to alleviate metabolic stress [11], while the sustained activation of the NER pathway and increased synthesis of antioxidant proteins impose substantial protein synthesis/folding pressure on ER. Consequently, this adaptive homeostasis is essentially a “high-cost, low-elasticity” balance [12]. Once compensatory mechanisms are overwhelmed, the adaptive homeostasis collapses, converting formerly protective responses into cytotoxic cascades that drive apoptosis [13]. Thus, precisely disrupting this adaptive homeostasis provides a crucial leverage point for reversing DDP resistance and devising synergistic therapeutic interventions.

With their surface programmability, structural diversity, and capacity for multifunctional integration, nanomedicines offer unique advantages for addressing the complex, multistep network underlying DDP resistance. Building on this concept, we designed a DDP-doped BP nanomedicine (DDP-BP@PDA) to effectively overcome tumor drug resistance by integrating the chemotherapeutic agent DDP onto the surface of piezoelectric BP nanosheets (BP NSs) and further modifying them with biocompatible polydopamine (PDA) to enhance stability and biocompatibility under physiological conditions (Figure 1). Mechanistically, DDP-BP@PDA disrupts the adaptive homeostatic network that sustains drug-resistant cell survival. It remodels the DDP internalization pathway, promoting intracellular drug accumulation and breaching the initial defense barrier of resistant cells. Under ultrasound (US) excitation, DDP-BP@PDA drove the oxidative consumption of glutathione (GSH) via piezoelectric catalysis, attenuating the detoxification capacity and thereby disrupting the redox homeostasis of drug-resistant cells. More importantly, piezoelectric polarization enhanced the peroxidase (POD)-like activity of the Pt single-atom nanozyme via electron injection, leading to substantial generation of ROS within drug-resistant tumor cells. The ROS burst disrupted the structure and function of surrounding proteins, significantly increasing the protein-folding burden of the ER. By compromising ER integrity and amplifying proteostatic stress, DDP-BP@PDA aggravates ER stress, thereby suppressing the expression of DNA repair proteins XPF and XPA, weakening DNA repair capacity. Consequently, under the combined cytotoxicity of DDP and ROS, drug-

resistant cells undergo extensive apoptosis. This work presents a therapeutic strategy that integrates traditional chemotherapy with single-atom piezoelectric nanomedicine to precisely disrupt adaptive homeostasis, offering mechanistic insights and a potential translational paradigm for overcoming chemoresistance in malignancies.

2 | Results and Discussion

We successfully synthesized BP NSs via ultrasonic liquid-phase exfoliation in N-methylpyrrolidone (NMP) [14], followed by in situ DDP loading and PDA coating to obtain BP@PDA and DDP-BP@PDA, respectively. Transmission electron microscopy (TEM) revealed that all three materials exhibited a sheet-like morphology (Figures 2a; S1 and S2). The lattice fringes observed in Figure 2b correspond to the (111) planes of BP crystals, while the distinct diffraction spots in the selected area electron diffraction (SAED) pattern can be indexed to the (021) crystal planes (Figure 2c), confirming the high crystallinity of the synthesized BP NSs. Importantly, DDP loading and PDA modification did not disrupt the crystalline structure of BP, thereby preserving its intrinsic piezoelectric properties. Aberration-corrected high-angle annular dark-field scanning TEM (AC-HAADF-STEM) images provided direct evidence that Pt was dispersed as isolated single atoms on the BP NSs (Figure 2d). Energy-dispersive X-ray spectroscopy (EDS) mapping further demonstrated the homogeneous distribution of Pt atoms on the nanosheet surface (Figure 2e,f). Fourier-transform infrared (FT-IR) spectrum (Figure 2g) showed a characteristic absorption peak at 1627 cm^{-1} assigned to P=O stretching vibration, while peaks at $\sim 2900\text{ cm}^{-1}$ correspond to C–H vibrations, validating the successful PDA coating. The N–H stretching band at $\sim 3286\text{ cm}^{-1}$ further confirmed the anchoring of DDP onto the BP surface [15, 16]. X-ray diffraction (XRD) patterns revealed sharp diffraction peaks corresponding to the characteristic crystal planes of BP, without detectable Pt-related peaks, excluding the presence of Pt clusters or nanoparticles (Figure 2h).

X-ray absorption spectroscopy (XAS) further elucidated the electronic state and local coordination environment of Pt in DDP-BP@PDA. As shown in Figure 2i, compared with Pt foil, DDP-BP@PDA exhibited an enhanced white-line intensity, indicative of a decreased occupancy of Pt 5d band [17]. Extended X-ray absorption fine structure (EXAFS) analysis in R-space revealed two distinct coordination shells: the first peak at $\sim 1.6\text{ \AA}$ corresponds to Pt–P bonding, while the second shell, attributed to Pt–Pt and Pt–Cl coordination, could not be readily distinguished due to their similar bond lengths (Figure 2j). Wavelet transform (WT)-EXAFS analysis revealed a local maximum at $R \approx 1.6\text{ \AA}$, $k \approx 5.2\text{ \AA}^{-1}$ in the first shell, and a maximum at $R \approx 2.5\text{ \AA}$, $k \approx 8.6\text{ \AA}^{-1}$ in the second shell. Although the R value of the second-shell Pt–Pt scattering in Pt foil is similar to that in DDP-BP@PDA, the distinct k values ($R = 2.7\text{ \AA}$, $k = 9.8\text{ \AA}^{-1}$ for Pt foil) indicate that the second-shell scattering in DDP-BP@PDA originates not from Pt–Pt, but from Pt–Cl coordination in unhydrated DDP (Figure 2k,l) [18]. This analysis strongly supports the atomic distribution of Pt without contributions from metallic Pt–Pt coordination. X-ray photoelectron spectroscopy (XPS) further corroborated the XAS findings, confirming that DDP is stably anchored on the BP surface in the form of divalent single atoms

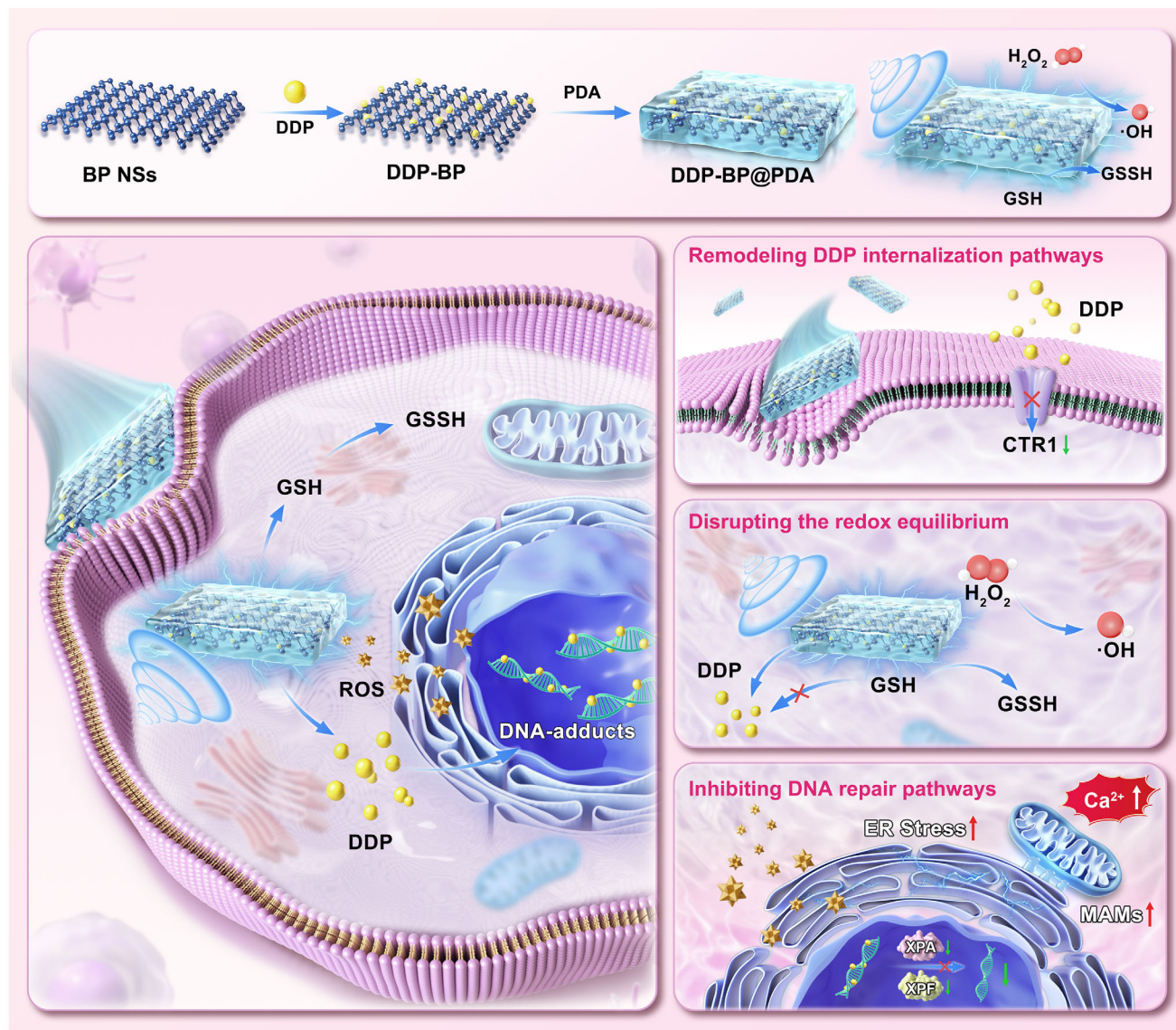


FIGURE 1 | Schematic illustration of the mechanism by which DDP-BP@PDA induces apoptosis in drug-resistant cells. Upon US activation, DDP-BP@PDA disrupts the adaptive homeostasis of DDP-resistant cells through piezocatalysis and polarization-enhanced nanozyme activity. Mechanistically, DDP-BP@PDA dismantles the three major defensive axes that sustain the resistant phenotype—attenuated drug uptake, reinforced detoxification capacity, and heightened DNA-repair competence. The collapse of these defenses renders resistant cells highly vulnerable to chemotherapeutic stress and ROS-induced damage, ultimately driving apoptotic cell death.

(Figure 2m–o). Collectively, these findings demonstrate that DDP is anchored to BP NSs as atomically dispersed Pt centers that partially coordinate with the BP surface. The retained DDP-derived, partially aquatable coordination environment preserves chemotherapeutic activity. Raman spectrum revealed that BP NSs, BP@PDA, DDP-BP@PDA, and Bulk BP all exhibited the three characteristic peaks (A^1_g , B_{2g} , A^2_g). Compared with Bulk BP, the peaks of BP NSs exhibited a slight blue shift, confirming the successful preparation of highly crystalline nanosheets. Moreover, no significant Raman shift was observed among BP NSs, BP@PDA, and DDP-BP@PDA, suggesting that neither DDP loading nor PDA modification destroyed the BP lattice structure (Figure 2p).

To evaluate the piezoelectric properties of BP NSs, we performed phase-voltage measurements using piezoresponse force

microscopy (PFM) [19]. BP NSs displayed a pronounced piezoelectric response under an applied voltage of 20 V. In addition to the characteristic butterfly-shaped hysteresis loop, the phase signal exhibited a 180° reversal within the DC voltage range of −20–+20 V, confirming the ferroelectric polarization switching (Figure S3) [20]. In addition to structural characteristics, efficient charge carrier migration is pivotal for piezocatalytic performance. Electrochemical impedance spectroscopy (EIS) revealed that DDP-BP@PDA possesses markedly lower charge-transfer resistance than BP@PDA (Figure S4), demonstrating that DDP doping substantially facilitates charge migration and thereby augments piezocatalytic activity (Figure 3a). To further validate the US-induced microscopic pressure-driven piezocatalytic effect, we employed the degradation of methylene blue (MB) as a model reaction, monitoring its time-dependent degradation under US irradiation and comparing the normalized absorption intensities

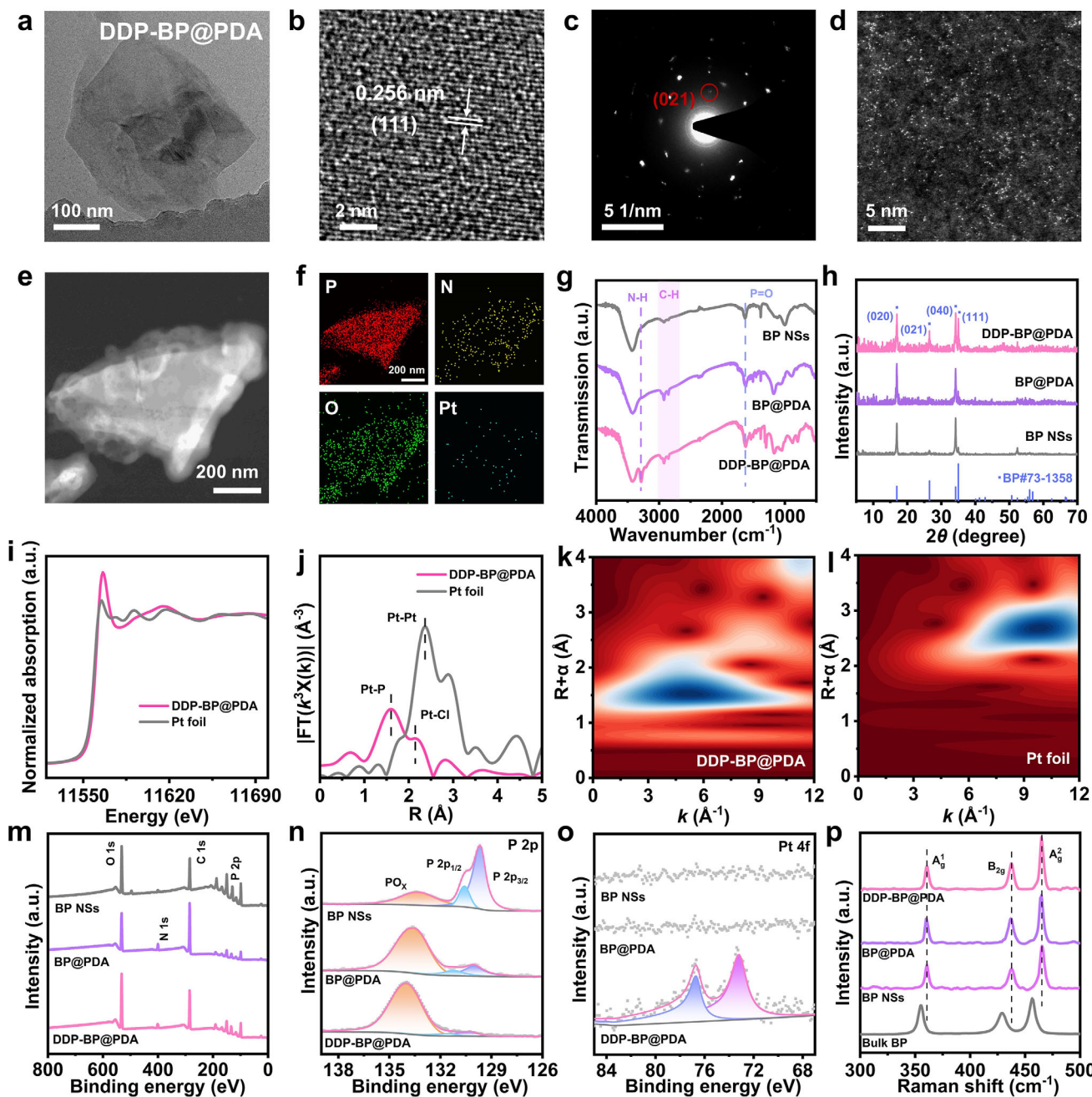


FIGURE 2 | Structural characterizations of DDP-BP@PDA. (a) TEM image of DDP-BP@PDA. (b) HRTEM image of DDP-BP@PDA. (c) The SAED pattern of DDP-BP@PDA. (d) AC-HAADF-STEM image of DDP-BP@PDA. (e, f) STEM image (e) with EDX mapping (f) of DDP-BP@PDA. (g) FT-IR spectra of BP NSs, BP@PDA and DDP-BP@PDA. (h) XRD patterns of BP NSs, BP@PDA and DDP-BP@PDA. (i, j) Normalized XANES spectra (i) and Fourier transform magnitudes in R space of the EXAFS at the Pt L_3 -edge (j) of DDP-BP@PDA and Pt foil. (k, l) EXAFS wavelet transform plots of DDP-BP@PDA (k) and Pt foil (l). (m) XPS spectrum of BP NSs, BP@PDA and DDP-BP@PDA. (n) High-resolution XPS spectra of P 2p. (o) High-resolution XPS spectra of Pt 4f. (p) Raman scattering spectra of the bulk BP, BP NSs, BP@PDA and DDP-BP@PDA.

at 664 nm across different treatment groups [21]. All experiments were conducted in the dark to exclude photodegradation. As anticipated, both BP@PDA+US and DDP-BP@PDA+US treatments led to a pronounced decrease in MB absorption intensity, confirming the piezocatalytic activity of BP (Figure S5). Notably, DDP-BP@PDA+US achieved the most substantial degradation, attributable to DDP doping, which enhanced the piezocatalytic performance of BP. GSH [22], which plays a central role in redox homeostasis, protects DDP-resistant cells by directly binding

to DDP and facilitating its efflux. To probe the role of GSH during piezocatalysis, we quantified GSH consumption using 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB). DTNB reacts with GSH to generate 5-thio-2-nitrobenzoic acid, which exhibits a characteristic absorption peak at 412 nm. Under US irradiation, the DDP-BP@PDA+US group showed significant GSH depletion, which was further exacerbated in the DDP-BP@PDA+US+ H_2O_2 group upon addition of hydrogen peroxide (H_2O_2) (Figures 3b and S6). These findings indicate that GSH acts as a sacrificial

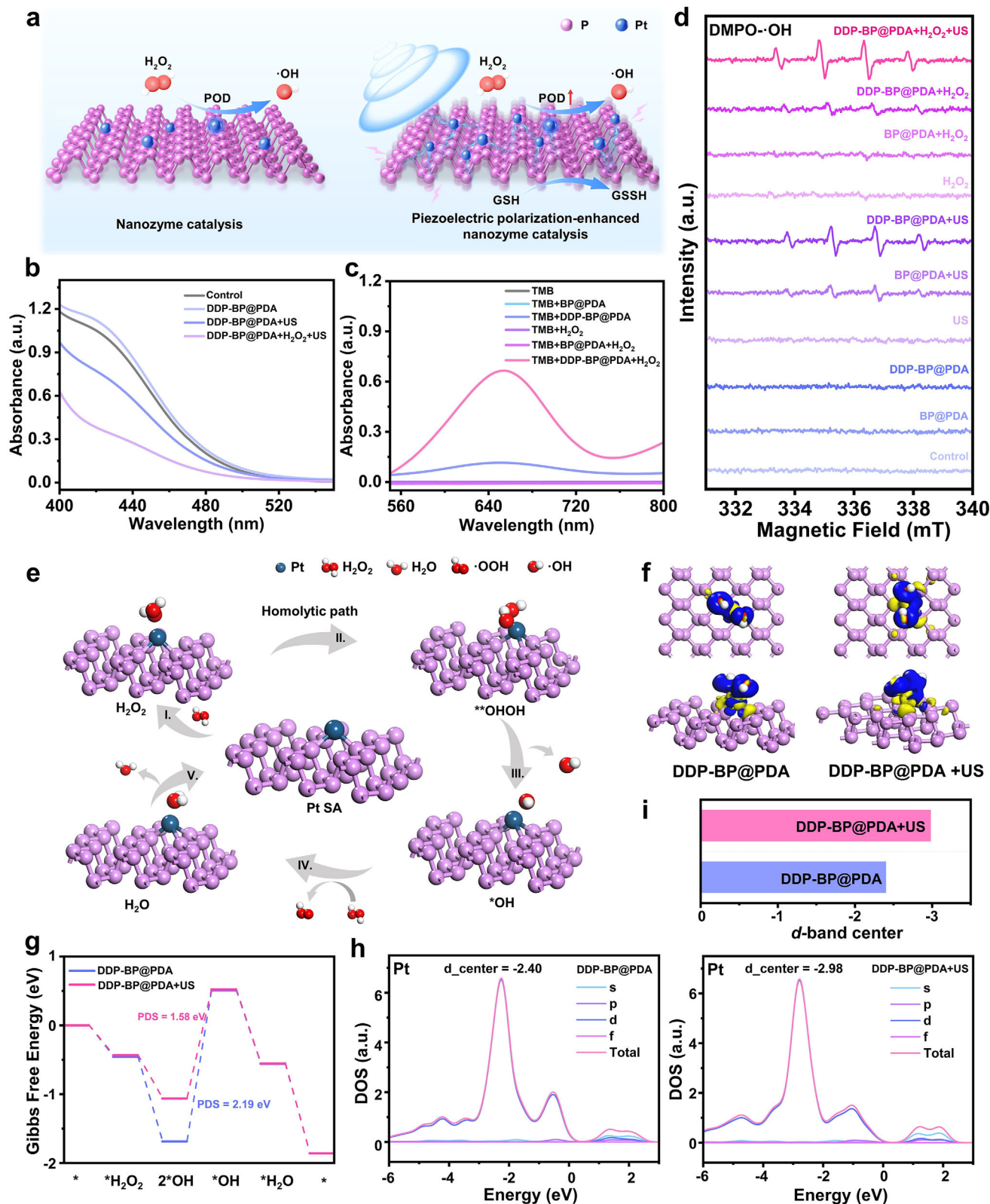


FIGURE 3 | Piezocatalytic and polarization-enhanced nanozyme performance and mechanisms of DDP-BP@PDA. (a) Schematic illustration of DDP-BP@PDA-mediated piezocatalysis and piezoelectric polarization-enhanced nanozyme-catalyzed reactions. (b) UV-Vis absorption spectra of GSH oxidation over time in different treatment groups. (c) UV-vis absorption spectra of catalyzed oxTMB from the different treatment groups. (d) EPR spectra of $\cdot\text{OH}$ trapped by 5,5-dimethyl-1-pyrroline-N-oxide (DMPO). (e) Catalytic mechanism for POD-like reaction on DDP-BP@PDA. (f) Differential charge density of DDP-BP@PDA-2 $\cdot\text{OH}$ and DDP-BP@PDA+US-2 $\cdot\text{OH}$ (the colors yellow and blue represent the increase and decrease of charge density, respectively). (g) Corresponding free energy diagram for POD-like catalytic reaction on DDP-BP@PDA under different conditions. (h) DOS of Pt for the model DDP-BP@PDA and DDP-BP@PDA+US. (i) d-band analysis of DDP-BP@PDA-2 $\cdot\text{OH}$ and DDP-BP@PDA+US-2 $\cdot\text{OH}$.

agent during piezocatalysis, thereby amplifying the catalytic effect (Figure S7).

Furthermore, the POD-like activity of DDP-BP@PDA was evaluated using a 3,3',5,5'-tetramethylbenzidine (TMB) colorimetric assay [23]. Analogous to Fenton-like reactions, in which H_2O_2 decomposes to generate hydroxyl radicals ($\cdot\text{OH}$), POD catalyzes the oxidation of TMB to blue ox-TMB using H_2O_2 as an electron acceptor. The results showed that DDP-BP@PDA alone did not induce obvious TMB oxidation in the absence of H_2O_2 . In contrast, pronounced TMB oxidation was observed only when H_2O_2 was present, indicating a typical H_2O_2 -dependent POD-like catalytic feature. More importantly, BP@PDA failed to efficiently catalyze TMB oxidation even in the presence of H_2O_2 , suggesting that the BP substrate itself is not the major active component responsible for the POD-like reaction (Figure 3c). To further quantify its enzyme-like catalytic behavior, we analyzed the steady-state POD-like activity of DDP-BP@PDA using Michaelis–Menten kinetics. The Michaelis constant (K_m) and maximum reaction velocity (V_{max}) were calculated to be 32.09 mM and 0.46 $\mu\text{M s}^{-1}$, respectively (Figure S8). To directly visualize $\cdot\text{OH}$ generation during piezocatalysis and polarization-enhanced nanozyme catalysis, electron spin resonance (ESR) spectroscopy was performed using 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) as a spin-trapping agent. US alone generated only a weak ROS signal, and ROS production under DDP-BP@PDA+US treatment was also relatively limited. By contrast, DDP-BP@PDA+US induced a markedly stronger ROS signal in the presence of H_2O_2 , which was substantially higher than that observed under US alone or DDP-BP@PDA+US conditions (Figure 3d). These results indicate that piezoelectric polarization significantly enhances POD-like activity of DDP-BP@PDA, thereby boosting $\cdot\text{OH}$ production.

To elucidate the mechanism underlying the piezoelectric polarization-driven enhancement of DDP-BP@PDA nanozyme catalysis, we performed density functional theory (DFT) calculations. For computational simplicity, the catalyst was assumed to be charge-neutral and solvent effects were neglected [24]. Figure 3e,g depict the key intermediates involved in the conversion of H_2O_2 to $\cdot\text{OH}$, together with the corresponding Gibbs free energy profiles, which reflect the POD-like activity of DDP-BP@PDA. H_2O_2 is first captured and spontaneously adsorbed onto the Pt atom of DDP-BP@PDA without energy input, followed by its decomposition into two surface-bound OH^* species. One $\cdot\text{OH}$ subsequently desorbs, resulting in a free-energy increase, while the other OH^* couples with a neighboring H^+ to form surface-adsorbed H_2O , a thermodynamically favorable process. The H_2O molecule then desorbs, restoring the system to its initial state. Free-energy analysis identifies the desorption of $\cdot\text{OH}$ as the potential rate-determining step. Notably, upon US application, the free-energy barrier at this step is substantially reduced for DDP-BP@PDA+US compared with pristine DDP-BP@PDA, indicating that the piezoelectric polarization accelerates the catalytic effect. To further elucidate the electronic mechanism of the piezoelectric polarization-enhanced POD activity, we examined the atomic orbital electronic properties of DDP-BP@PDA and DDP-BP@PDA+US. Charge-density difference analysis (Figure 3f) shows that US weakens the adsorption of 2^*OH species, thereby facilitating subsequent reactions. Moreover, the *d*-band center of DDP-BP@PDA, located at -2.40 eV, shifts downward to -2.98 eV in

DDP-BP@PDA+US (Figure 3h,i). According to *d*-band theory, a *d*-band center closer to the Fermi level corresponds to stronger adsorption of reaction intermediates [25]. Thus, piezoelectric polarization tunes the adsorption strength of OH^* on DDP-BP@PDA, facilitates subsequent proton-coupled steps, and ultimately enhances overall catalytic performance.

Typically, the maintenance of DDP resistance involves multiple synergistic mechanisms, including reduced drug uptake, enhanced detoxification, and increased tolerance to DNA adducts [26]. Here, we first investigated whether DDP-BP@PDA could eliminate B16-F10/DDP cells by disrupting their adaptive homeostasis (Figure 4a). Under prolonged platinum-based chemotherapy, the copper transporter CTR1, which mediates DDP uptake, is markedly downregulated, leading to diminished intracellular drug accumulation. Consistent with this, CTR1 expression was significantly lower in B16-F10/DDP cells than in B16-F10 cells (Figure 4b,c) [27], correlating with a pronounced reduction in free DDP uptake. To quantitatively verify this difference, we measured intracellular Pt levels by ICP-MS after free DDP treatment. B16-F10/DDP cells exhibited markedly lower intracellular Pt accumulation than B16-F10 cells, confirming impaired DDP uptake (Figure S9). To further define the cellular internalization mechanism of DDP-BP@PDA, we performed uptake studies using a panel of classical endocytosis inhibitors. Pretreatment with EIPA or genistein markedly reduced the uptake of CY2-DDP-BP@PDA in B16-F10/DDP cells, whereas chlorpromazine produced only a modest effect, indicating that DDP-BP@PDA is internalized predominantly through macropinocytosis and caveolae-dependent endocytosis (Figure S10). Confocal imaging further confirmed that uptake of the DDP-Cyanine2 (CY2) was significantly diminished in B16-F10/DDP compared to B16-F10 after 4 h (Figure 4e,f). Strikingly, when DDP was delivered via DDP-BP@PDA, intracellular accumulation was substantially enhanced through an endocytic pathway, as verified by flow cytometry and confocal imaging (Figure 4d–f) [28]. Consistently, further ICP-MS analysis showed that DDP-BP@PDA treatment led to markedly higher intracellular Pt accumulation in B16-F10/DDP cells than free DDP (Figure S11). GSH, a central antioxidant molecule that maintains cellular redox homeostasis, also constitutes a key molecular basis of adaptive resistance in DDP-resistant cells. Lowering intracellular GSH levels can effectively impair the detoxification and antioxidant defenses of the resistant cells. We therefore measured intracellular GSH levels. Compared with the control, DDP-BP@PDA+US treatment markedly reduced intracellular GSH content (Figure 4g), indicating that US-activated DDP-BP@PDA promotes GSH depletion and thereby compromises the antioxidant defence capacity of resistant cells. Furthermore, the levels of intracellular ROS were determined using the DCFH-DA probe by CLSM (Figure 4j,k), demonstrating a pronounced increase in intracellular ROS following DDP-BP@PDA+US treatment. Thus, under in situ US stimulation, DDP-BP@PDA can disrupt the antioxidant defenses and generate substantial ROS, thereby remodeling redox homeostasis. To further verify whether DDP-BP@PDA could restore DDP sensitivity, intracellular Pt-DNA adducts were quantified using ICP-MS (Figure 4h,i). Compared with free DDP, both DDP-BP@PDA and DDP-BP@PDA+US treatments significantly enhanced adduct formation, with the highest levels observed in the DDP-BP@PDA+US group. These findings demonstrate that DDP-BP@PDA restores the sensitivity of resistant cells to

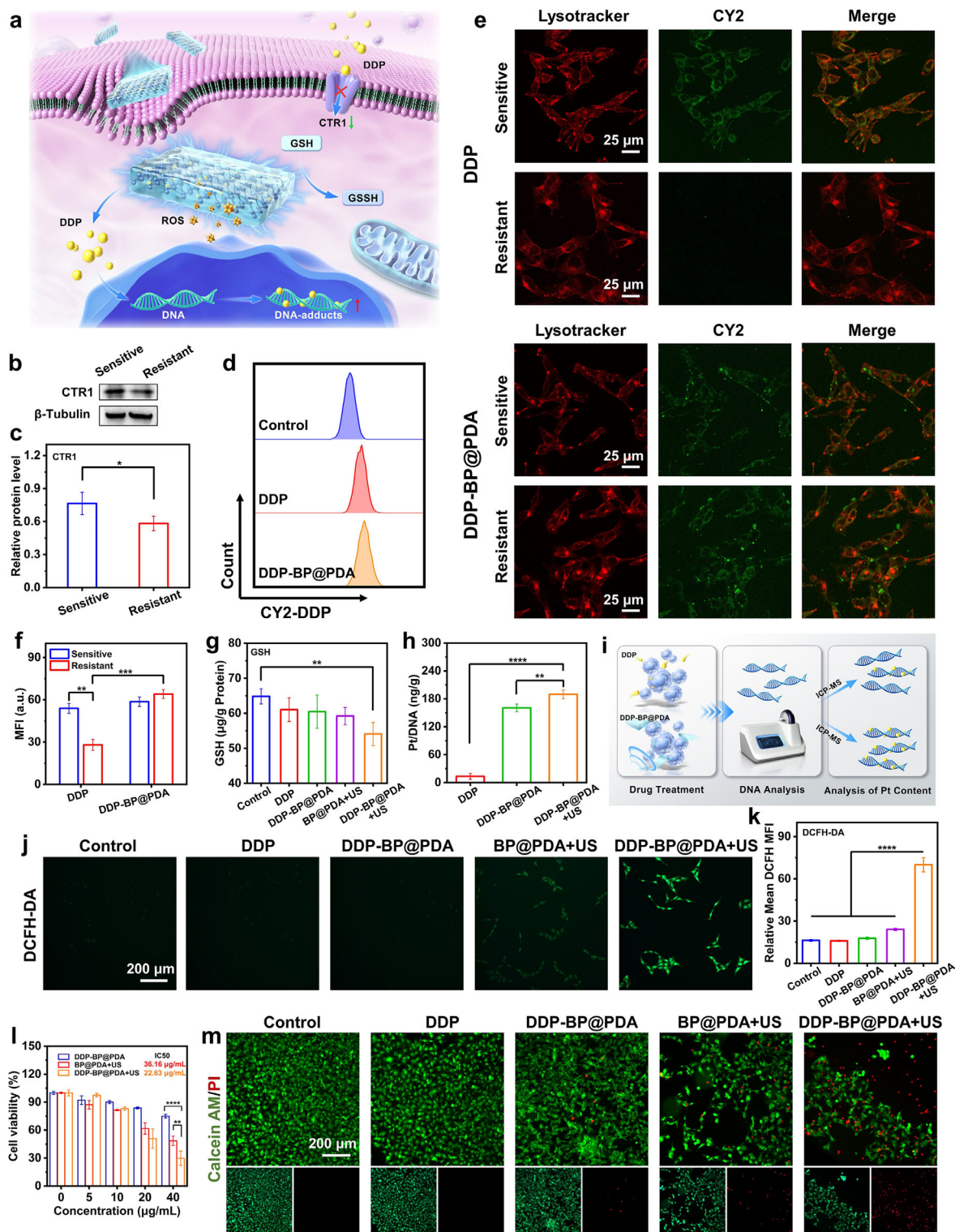


FIGURE 4 | The synergistic therapeutic effect of DDP-BP@PDA. (a) Schematic illustration of the therapeutic process of DDP-BP@PDA in B16-F10/DDP cells. (b) Western blot analysis of CTR1 protein expression. (c) Semiquantitative analysis of CTR1 expression from (b). (d) Flow cytometry of intracellular CY2-DDP in B16-F10/DDP cells after different treatments. (e) CLSM images of intracellular localization of CY2-DDP and CY2-DDP-BP@PDA after 4 h incubation and (f) corresponding quantitative analysis. (g) Intracellular GSH content in B16-F10/DDP cells after different treatments (mean ± SD, n = 3 independent experiments). (h, i) Formation of Pt-DNA adducts after different treatments at Pt-equivalent concentrations (mean ± SD, n = 3 independent experiments). (j) Fluorescence images of intracellular ROS levels (DCFH-DA staining) in B16-F10/DDP cells and (k) corresponding quantitative analysis (mean ± SD, n = 3 independent experiments). (l) Viability of B16-F10/DDP cells under various treatments (mean ± SD, n = 3 independent experiments). (m) Fluorescence images of live (Calcein-AM, green) and dead (PI, red) B16-F10/DDP cells after different treatments. The statistical significance analysis was determined using Student's t-test (two-group analysis) or one-way analysis of variance (ANOVA) (multigroup analysis). ns not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

DDP by augmenting intracellular drug uptake and DDP-mediated cytotoxicity [29]. Cytotoxicity assays further corroborated these results. We first assessed the cytocompatibility of DDP-BP@PDA toward normal cells using L929 fibroblasts as a representative model. In the CCK-8 assay, DDP-BP@PDA showed negligible cytotoxicity at the therapeutic concentration, with L929 cell viability remaining high (Figure S12), indicating good compatibility with normal cells under the tested conditions. We then evaluated the therapeutic cytotoxicity against B16-F10/DDP cells. DDP-BP@PDA combined with US produced the most pronounced cytotoxic effect, whereas DDP-BP@PDA alone showed only limited activity, likely because its POD-like catalytic activity was insufficient to generate enough ROS to destabilize the adaptive homeostasis of resistant cells. No significant cytotoxicity was observed with US or BP@PDA alone (Figures 4l and S13–S15). Consistent with these results, Calcein-AM/PI staining revealed that DDP-BP@PDA+US induced the highest proportion of cell death (Figure 4m), demonstrating that DDP-BP@PDA under US stimulation can effectively disrupt the adaptive homeostasis of DDP-resistant cells and restore their chemosensitivity.

To elucidate the molecular mechanisms by which DDP-BP@PDA+US overcomes tumor resistance through disruption of adaptive homeostasis in DDP-resistant cells, we conducted RNA-seq analysis of drug-resistant tumor cells following treatment. Principal component analysis (PCA) and correlation heatmaps confirmed strong biological reproducibility and clear separation between groups, underscoring high data quality and treatment-induced transcriptomic reprogramming (Figure 5a,b). Differential expression analysis identified 3849 upregulated and 3347 downregulated genes (Figure 5c), with Venn diagram analysis highlighting the overlap between groups (Figure 5d). Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment revealed that these genes were predominantly associated with oxidative stress, apoptosis, cell cycle regulation, and DNA repair pathways (Figure 5e). Given that platinum drugs exert their efficacy largely through induction of intrastrand DNA cross-links, the Gene Ontology (GO) analysis was particularly notable: differentially expressed genes were enriched in processes related to DNA binding, damage, and repair (Figure 5f), while the HALLMARK DNA repair gene set was globally suppressed (Figure 5g). These findings suggest that DDP-BP@PDA enhances DDP sensitivity by inhibiting DNA repair pathways, thereby disrupting the adaptive resistance of tumor cells. In addition, GO analysis revealed marked effects on cellular stress responses and protein synthesis. Cellular component and biological process analysis of ER indicated substantial perturbations in ER structure and function, including calcium overload, activation of the unfolded protein response, and intrinsic apoptotic signaling pathway in response to ER stress (Figure 5i) [10]. Protein-protein interaction analysis further demonstrated dense interconnectivity among these key regulators (Figure 5h). Finally, qPCR validation corroborated the transcriptomic findings, showing that DDP-BP@PDA+US elevated stress levels in resistant cells, concurrently inducing structural and functional disruption of the ER, which in turn downregulated DNA repair-related genes and triggered apoptosis in drug-resistant tumor cells (Figure 5j).

To elucidate the mechanism by which DDP-BP@PDA amplifies stress in DDP-resistant cells to disrupt their adaptive homeostasis

and suppress enhanced DNA repair, we initiated our investigation at the organelle level. Transcriptomic analysis directed our focus to ER stress. Comparative assessment revealed that B16-F10/DDP experiences markedly heightened ER stress compared to B16-F10, indicating that long-term DDP exposure maintains them in a state of chronic ER stress (Figure S16). This adaptive compensation may serve as a potential therapeutic target to reverse resistance and promote apoptosis [5]. Based on these observations, we hypothesized that DDP-BP@PDA could exacerbate ER stress in resistant cells by disrupting redox homeostasis, thereby inhibiting DNA repair pathways and resensitizing cells to DDP. To test this hypothesis, we evaluated the expression of canonical ER stress and apoptosis markers (p-PERK, ATF4, and CHOP) across different treatment groups (Figure 6a,b) [10]. Both BP@PDA+US and DDP-BP@PDA+US significantly upregulated these proteins, with the strongest ER stress induction observed in the DDP-BP@PDA+US group, indicating that DDP-doped BP piezoelectric nanomedicine amplifies ER stress to disrupt the maintenance of adaptive homeostasis and restore DDP sensitivity.

Mitochondria-associated ER membranes (MAMs) are crucial for cellular homeostasis, regulating calcium signaling, lipid metabolism, and energy production [30]. Under ER stress, cells typically expand ER-mitochondrial contacts to facilitate Ca^{2+} transfer and metabolic support, mitigating stress [31]. However, excessive stress drives aberrant Ca^{2+} flux, triggering mitochondrial dysfunction, and converting MAMs from protective hubs into “amplifiers” of damage and apoptosis. TEM revealed that DDP-BP@PDA+US treatment markedly increased ER-mitochondrial contacts (Figures 6c and S17), which was further corroborated by colocalization analysis using ER-tracker and mito-tracker (Figure 6d). These results indicate that DDP-BP@PDA+US can significantly amplify ER stress in drug-resistant cells. Both redox imbalance and excessive ER stress can precipitate mitochondrial dysfunction, often accompanied by elevated cytoplasmic Ca^{2+} . We employed the JC-1 probe to evaluate mitochondrial membrane potential (MMP) in B16-F10/DDP cells. DDP treatment induced only a mild reduction in MMP, as reflected by a slight decrease in red fluorescence in CLSM images. In contrast, cells treated with DDP-BP@PDA or BP@PDA+US exhibited a pronounced decrease in red fluorescence accompanied by an increase in green JC-1 monomers, indicating substantial mitochondrial dysfunction. Notably, the DDP-BP@PDA+US group showed the most pronounced effect, with the highest accumulation of green fluorescence, demonstrating that this treatment induced the most severe mitochondrial impairment (Figure 6g,h). Furthermore, we measured cytoplasmic Ca^{2+} in B16-F10/DDP cells using the Fluo-4 indicator. Excessive ER stress significantly elevated cytoplasmic Ca^{2+} relative to control (Figure 6e,f). Collectively, these results demonstrate that DDP-BP@PDA+US amplifies cellular stress by enhancing ER stress, increasing ER-mitochondrial contacts, inducing mitochondrial dysfunction, and promoting Ca^{2+} overload. This multifaceted perturbation disrupts the adaptive homeostasis of DDP-resistant cells, thereby restoring their sensitivity to DDP [32].

As the primary site for protein synthesis and folding, the ER plays a critical role in maintaining cellular proteostasis. Excessive ER stress can profoundly disrupt proteostasis, thereby compromising the adaptive homeostasis upon which DDP-resistant cells depend for survival [33]. DDP exerts cytotoxicity primarily by inducing

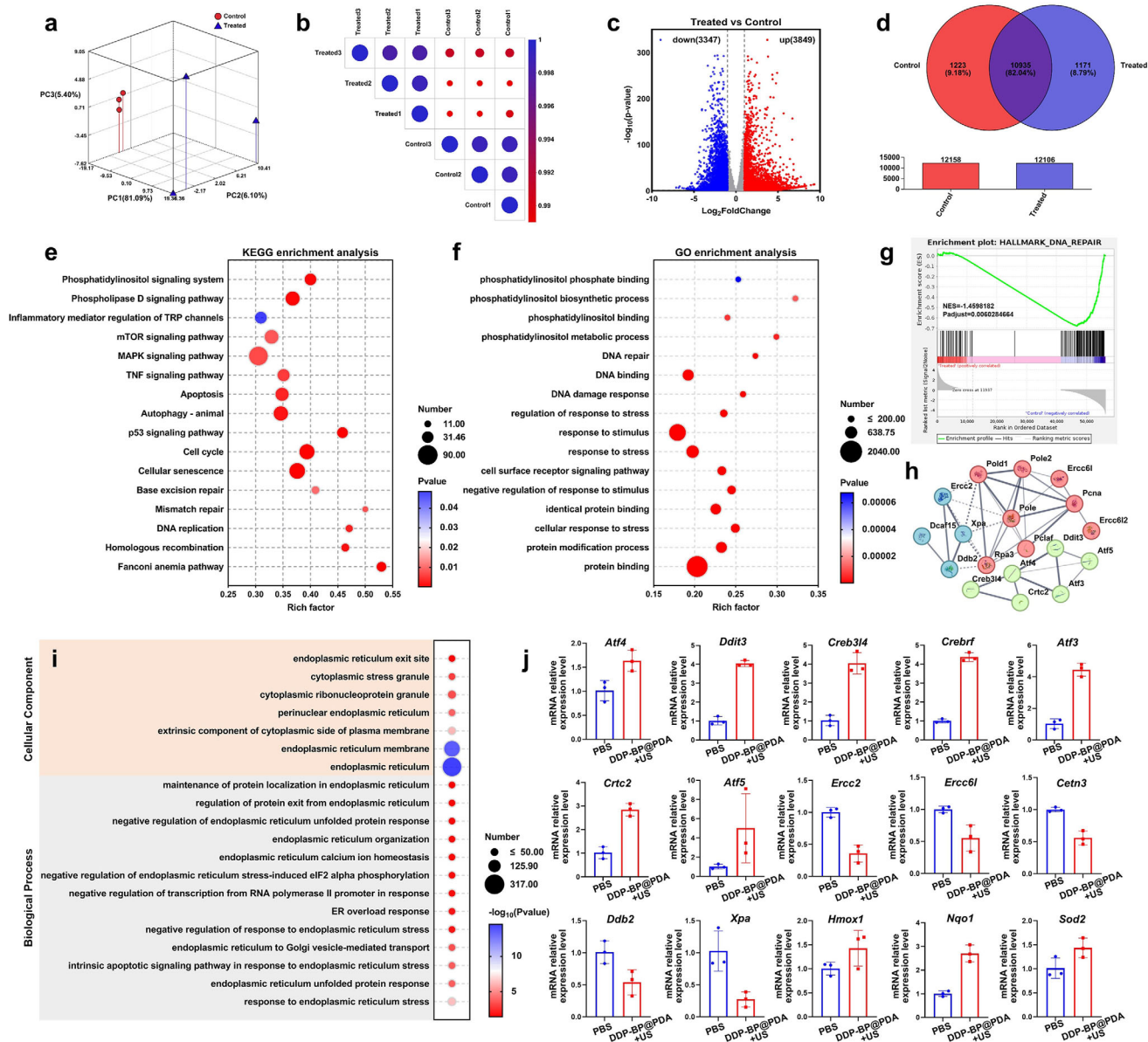


FIGURE 5 | RNA-seq analysis of B16-F10/DDP cells treated with PBS and DDP-BP@PDA+US. (a) Principal component analysis (PCA) plot showing the transcriptomic profiles of PBS (Control) and DDP-BP@PDA+US (Treated) groups. (b) Heatmap of pairwise Pearson correlation coefficients between samples. The color key indicates the correlation value, with blue representing high similarity. (c) Volcano plot of differentially expressed genes (DEGs) in the DDP-BP@PDA+US group compared with the PBS group. Each dot represents a single gene. Red represents upregulated genes. Blue represents downregulated genes. FC, fold change. (d) Venn diagram illustrating the overlap of DEGs identified from the comparisons of PBS (red) and DDP-BP@PDA+US (blue). (e) Bubble plot of KEGG pathway enrichment analysis of the DEGs between the PBS and DDP-BP@PDA+US groups. The size of the bubbles is proportional to the number of differentially highly expressed genes assigned to the KEGG term. (f) GO enrichment analysis of DEGs, showing the most significantly enriched categories. The size of the bubbles is proportional to the number of differentially highly expressed genes assigned to the GO term. (g) Gene Set Enrichment Analysis (GSEA) plot, Enrichment plot for the [HALLMARK DNA REPAIR] gene set. (h) The protein-protein interaction (PPI) network of DEGs in the PBS and DDP-BP@PDA+US groups. (i) Gene Ontology (GO) enrichment analysis reveals significant enrichment of ER-associated terms in the Cellular Component and Biological Process categories. (j) RT-qPCR of relevant markers in B16-F10/DDP cells. Error bars represent standard deviation based on three replicate data ($n = 3$ independent experiments).

intrastrand DNA cross-links, while drug-resistant cells counteract these effects through enhanced DNA repair mechanisms. Under US, DDP-BP@PDA exacerbates ER stress and suppresses the translation of DNA repair enzymes, thereby restoring DDP sensitivity in resistant cells. Notably, key components of the NER pathway, XPF and XPA, are typically upregulated in resistant cells (Figure S18) [34]. Western blot analysis revealed

that their expression remained high in the control, DDP, and DDP-BP@PDA groups, but was markedly reduced following DDP-BP@PDA+US treatment, while BP@PDA+US induced only a modest decrease (Figure 6i). Statistical analysis confirmed significant downregulation of XPF and XPA in B16-F10/DDP cells treated with DDP-BP@PDA+US (Figure 6j), and immunofluorescence staining of XPF and XPA corroborated these findings

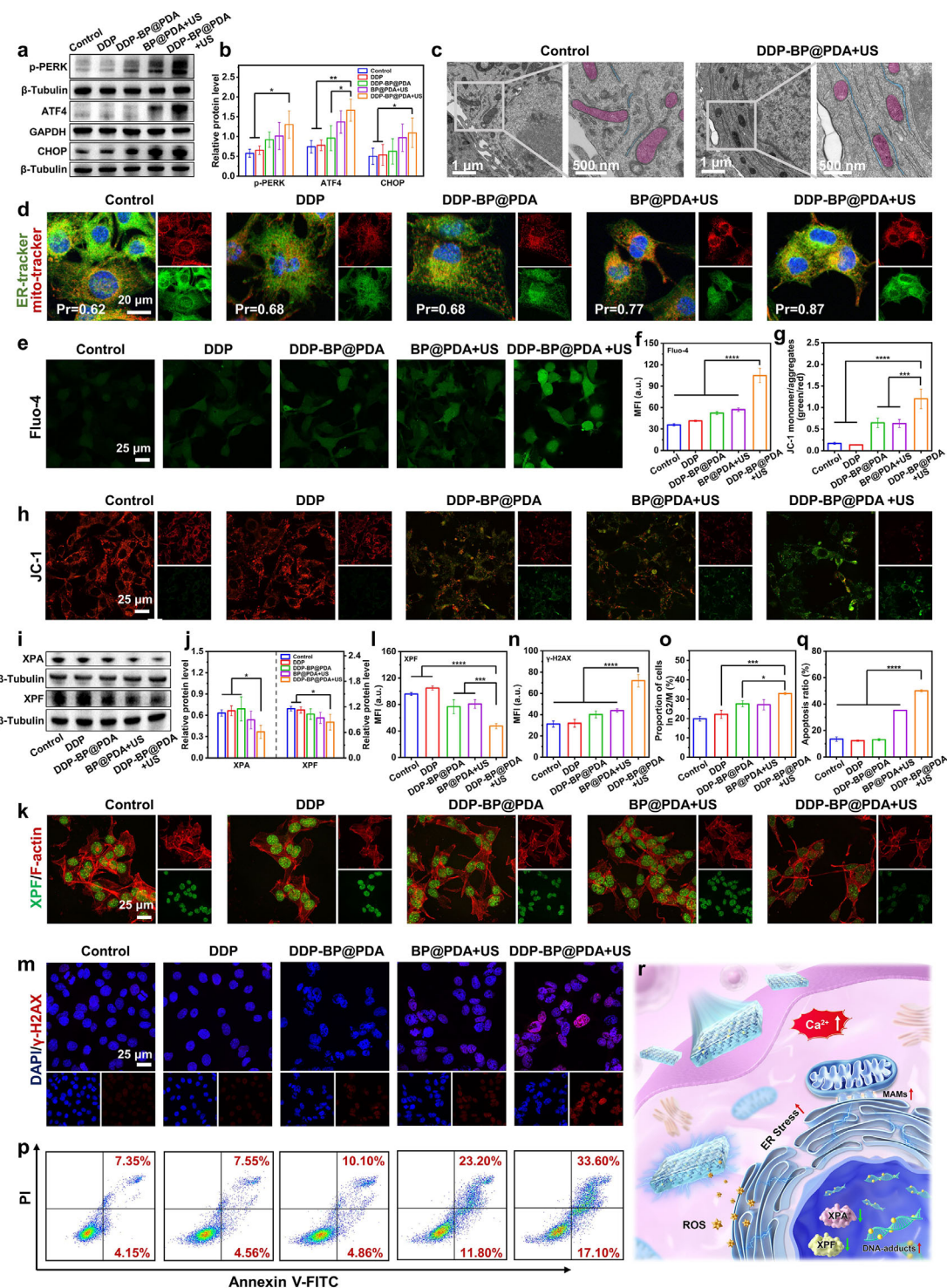


FIGURE 6 | Mechanistic analysis of DDP-BP@PDA in B16-F10/DDP cells. (a) Western blot analysis of p-PERK, ATF4, and CHOP expression. (b) Semiquantitative analysis of p-PERK, ATF4, and CHOP levels from (a). (c) Representative TEM images showing ER-mitochondria contacts in untreated (Control) or DDP-BP@PDA+US-treated cells. (d) Representative confocal images of B16-F10/DDP cells after different treatments, with nuclei (Hoechst 33342, blue), ER (ER-Tracker, green), and mitochondria (Mito-Tracker, red), and quantification of ER-mitochondria colocalization. (e,f) CLSM images and quantitative analysis of Fluo-4 staining after different treatments. (g,h) CLSM images of JC-1 staining and corresponding green/red fluorescence ratios in B16-F10/DDP cells. (i) Western blot analysis of XPA and XPF expression. (j) Semiquantitative analysis of XPA and XPF levels from (i). (k,l) CLSM images of XPF expression in B16-F10/DDP cells and corresponding quantification. (m,n) CLSM images of γ -H2AX expression in B16-F10/DDP cells and corresponding quantification. (o) G2/M ratio of B16-F10/DDP cells analyzed by flow cytometry. (p,q) Flow cytometry analysis of apoptosis in B16-F10/DDP cells after different treatments using annexin V-FITC/PI staining. (r) Schematic illustration of the therapeutic mechanism of DDP-BP@PDA. Error bars represent standard deviation based on three replicate data ($n = 3$ independent experiments). The statistical significance analysis was determined using Student's t-test (two-group analysis) or one-way analysis of variance (ANOVA) (multigroup analysis). ns not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

(Figures 6k,l and S19). To further define the relationship between amplified ER stress and the suppression of DNA repair protein expression, we used 4-phenylbutyric acid (4-PBA) to alleviate ER stress and AMG PERK 44 to inhibit the PERK branch of the unfolded protein response. In parallel, thapsigargin was used to induce ER stress in the absence of DDP-BP@PDA. Alleviation of ER stress effectively rescued the DDP-BP@PDA+US-induced decrease in XPF expression, whereas thapsigargin alone was sufficient to reduce XPF expression (Figure S20). Together, these results indicate that DDP-BP@PDA+US suppresses DNA repair-associated protein expression by amplifying ER stress, thereby disrupting the dynamic balance between DNA damage and repair in cisplatin-resistant cells and ultimately restoring their sensitivity to DDP.

To further define the origin of the therapeutic effects induced by DDP-BP@PDA+US and determine whether they arise from the coordinated integration of multiple activities, we constructed two mechanistic controls using the same preparation strategy and Pt feeding amount as those used for DDP-BP@PDA: Pt-BP@PDA, prepared with chloroplatinic acid as the non-DDP Pt source, and DDP-GO@PDA, in which graphene oxide was used as a non-piezoelectric carrier. We then evaluated their effects on ER stress amplification and DNA repair suppression (Figures S21 and S22). DDP-BP@PDA+US induced the most pronounced upregulation of ATF4 and the strongest downregulation of XPF. By contrast, although DDP-GO@PDA+US was able to deliver DDP, its capacity to amplify ER stress and suppress XPF expression was markedly weaker than that of DDP-BP@PDA+US, owing to the absence of BP piezoelectric polarization-mediated catalytic enhancement. These findings indicate that the therapeutic activity of DDP-BP@PDA+US cannot be attributed solely to DDP delivery or Pt-associated components, but instead depends on the synergistic coupling of DDP delivery, BP-mediated enhanced catalytic reaction, and ER stress amplification. We next examined whether DDP-BP@PDA+US could elicit comparable effects in SKOV3/DDP and A549/DDP cells (Figure S23). Consistent with the observations in B16-F10/DDP cells, DDP-BP@PDA+US effectively amplified ER stress and suppressed XPF expression in both resistant cell lines, suggesting that this effect is not restricted to a single DDP-resistant model. Together, these results support adaptive homeostasis disruption as a potentially generalizable strategy for overcoming DDP resistance.

To determine whether the cytotoxic effect of DDP-BP@PDA on drug-resistant cells is associated with DNA damage, we evaluated DNA damage across different treatment groups. Immunostaining for γ -H2AX revealed that DDP-BP@PDA+US treatment markedly increased DNA damage in resistant cells (Figure 6m,n). Under excessive ER stress, DNA damage and ER stress can establish a self-reinforcing feedback loop, ultimately driving cell cycle arrest and apoptosis. Meanwhile, flow cytometry analysis showed that DDP-BP@PDA+US treatment significantly increased the proportion of cells in the G2/M phase (Figures 6o and S24). Moreover, apoptosis assays using PI and FITC double staining demonstrated that the apoptotic rate rose from 11.5% in the control group to 50.7% following DDP-BP@PDA+US treatment (Figure 6p,q). In summary, these results indicate that the therapeutic efficacy of DDP-BP@PDA against DDP-resistant tumor cells arises from the amplification of cellular stress induced by piezoelectric effects and polarization-enhanced

nanozyme catalysis. This amplified stress disrupts the adaptive homeostasis of resistant cells, suppressing critical pathways that sustain resistance, including DNA repair and DDP detoxification, ultimately restoring their sensitivity to DDP (Figure 6r).

Before systematically evaluating the *in vivo* clearance of drug-resistant cells by DDP-BP@PDA, we performed a comprehensive assessment of its systemic acute toxicity to confirm its biosafety (Figure 7a). Female C57BL/6 mice were intravenously administered DDP-BP@PDA at varying doses (0, 20, and 50 mg kg⁻¹) for acute toxicity testing. Throughout the 14-day observation period, no abnormal clinical signs were observed, and body weight trajectories in the treated groups closely paralleled those of the control group (Figure S25). At day 14 post-injection, blood biochemical analyses demonstrated that liver and kidney function markers, including lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine (CREA), creatine kinase (CK), and UREA, remained within normal ranges and showed no significant differences compared with controls (Figures 7b–f and S26). Hematological examinations further revealed that indices such as white blood cell (WBC), platelet (PLT), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), hematocrit (HCT), red blood cell count (RBC), and hemoglobin (HGB) were unaffected by DDP-BP@PDA administration across all tested doses, remaining within physiological ranges (Figures 7g–l and S27). In addition, histopathological analysis via hematoxylin-eosin (H&E) staining of major organs (heart, liver, spleen, lung, and kidney) revealed no detectable abnormalities, thereby corroborating the excellent biocompatibility of DDP-BP@PDA (Figure S28).

Inspired by the pronounced anticancer activity of DDP-BP@PDA at the cellular level, we next assessed its therapeutic potential against drug-resistant tumors *in vivo* using a B16-F10/DDP subcutaneous xenograft model (Figure 7m). Once tumors reached ~50 mm³, tumor-bearing C57BL/6 mice were randomly assigned to five groups ($n = 5$ per group): control (PBS), DDP, DDP-BP@PDA, BP@PDA+US, and DDP-BP@PDA+US (10 mg kg⁻¹), to systematically evaluate therapeutic efficacy. Over the 13-day treatment period, mice received intratumoral injection of DDP-BP@PDA on days 0, 2, and 4, followed by US irradiation 4 h later. Tumor growth curves revealed rapid progression in the DDP group, comparable to the control group, whereas the DDP-BP@PDA and BP@PDA+US groups exhibited moderate inhibition. In sharp contrast, the DDP-BP@PDA+US group achieved the most pronounced suppression, attributable to its piezoelectric catalysis and synergism with chemotherapy (Figures 7n,o and S29). At treatment endpoint, tumors in the DDP-BP@PDA+US group weighed significantly less than those in all other groups (Figure 7p,q), with the highest inhibition rate (90.9%) compared to 42.1% in the DDP-BP@PDA group, and 58.2% in the BP@PDA+US group (Figure 7r). Importantly, body weights remained stable across groups, and no histopathological abnormalities were observed in major organs (heart, liver, spleen, lung, and kidney), confirming the biosafety of DDP-BP@PDA-based therapy (Figures 7s and S30). Furthermore, we evaluated the *in vivo* antitumor efficacy of systemically administered DDP-BP@PDA-FA (folate), with an equivalent dose of free DDP delivered via tail-vein injection included as an additional control

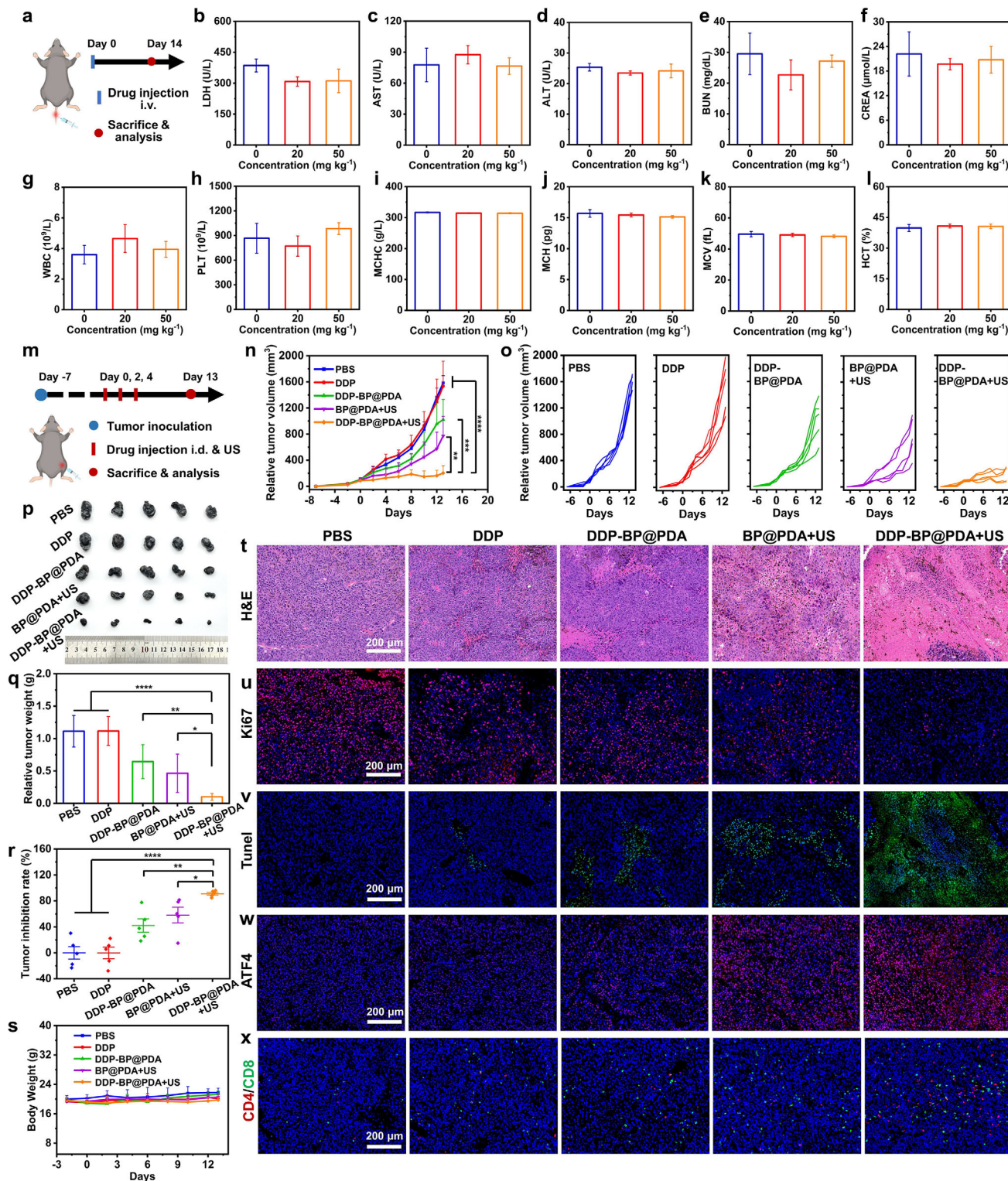


FIGURE 7 | In vivo biosafety and antitumor efficacy of DDP-BP@PDA. (a) Schematic illustration of the acute toxicity study of DDP-BP@PDA. (b–f) Blood biochemistry and (g–l) blood routine indexes on day 14 after intravenous injection of DDP-BP@PDA at different doses (0, 20, or 50 mg kg⁻¹). Data are shown as mean ± SD (n = 3 independent experiments). (m) Schematic illustration of the establishment and treatment of the B16-F10/DDP tumor-bearing mouse model. (n) Average tumor growth curves in mice following different treatments (n = 5). (o) Individual tumor growth curves corresponding to (n). (p) Photographs of excised B16-F10/DDP tumors on day 13 after treatment. (q) Tumor weights after the indicated treatments. (r) Tumor inhibition rates at the end of treatment. (s) Body-weight dynamics of tumor-bearing mice during treatment. (t–y) Representative histological images of tumor sections stained with H&E (t), Ki67 (u), TUNEL (v), ATF4 (w), and CD4⁺/CD8⁺ T cells (x). The statistical significance analysis was determined using Student's t-test (two-group analysis) or one-way analysis of variance (ANOVA) (multigroup analysis). ns not significant, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

(Figure S31). The results showed that DDP-BP@PDA-FA +US still markedly inhibited tumor growth after systemic administration, with an overall therapeutic trend consistent with that observed in the intratumoral injection model. More importantly, compared with the more clinically relevant systemic free-DDP regimen, DDP-BP@PDA-FA+US exhibited stronger tumor growth inhibition. To clarify the relative contributions of free DDP and BP@PDA, we introduced a DDP+BP@PDA+US group in both in vitro and in vivo treatment studies, with DDP and BP@PDA doses matched to those in the DDP-BP@PDA+US group (Figure S32). Notably, DDP-BP@PDA+US consistently produced the strongest antitumor efficacy in vitro and in vivo, outperforming the physical combination of free DDP and BP@PDA. These results indicate that the enhanced therapeutic outcome does not simply arise from the additive effects of individual components, but rather from the integrated synergy between DDP delivery and the piezoelectric activity of BP.

To elucidate the underlying mechanism, we performed systematic histological and immunological analyses. H&E staining, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling (Tunel) staining, and Ki67 immunostaining (Figure 7t–v), demonstrated that the DDP-BP@PDA+US group exhibited the most extensive necrosis, the strongest apoptotic signal, and the lowest proliferative index, indicating potent suppression of drug-resistant tumor cell growth. Immunofluorescence analysis further revealed elevated expression of ATF4 in the DDP-BP@PDA+US group, consistent with marked ER stress (Figure 7w), in agreement with in vitro findings. Additionally, CD4/CD8 immunofluorescence analysis showed that DDP-BP@PDA+US markedly enhanced intratumoral T-cell infiltration and promoted differentiation into cytotoxic CD4⁺ and CD8⁺ T cells, signifying robust activation of antitumor immunity within drug-resistant tumors (Figure 7x) [35]. Quantitative analysis confirmed that DDP-BP@PDA+US significantly increased the proportions of intratumorally CD4⁺ and CD8⁺ T cells. In parallel, the expression levels of the functional immune markers granzyme B and IFN- γ were markedly elevated, indicating enhanced cytotoxic and antitumor effector functions of the infiltrating T cells (Figure S33). To determine whether T cells functionally contributed to the therapeutic efficacy of DDP-BP@PDA-FA+US, we further performed T-cell depletion experiments (Figure S31). Depletion of CD8⁺ T cells markedly attenuated DDP-BP@PDA-FA+US-mediated tumor growth inhibition, indicating that CD8⁺ cytotoxic T cells functionally contribute to the antitumor response. To further assess whether this treatment could elicit systemic antitumor immunity, we established distant tumor and tumor rechallenge models. In the distant tumor model (Figure S34), local DDP-BP@PDA+US treatment not only inhibited the growth of directly treated primary tumors, but also delayed the progression of untreated distant tumors, indicating the induction of a systemic antitumor immune response. In the tumor rechallenge model (Figure S35), mice whose tumors were controlled after DDP-BP@PDA+US treatment showed stronger resistance to subsequent tumor cell rechallenge, suggesting the establishment of early antitumor immune memory. Together, these results demonstrate that under US stimulation, DDP-BP@PDA amplifies the stress responses of drug-resistant cells via the piezoelectric effect, thereby disrupting their adaptive homeostasis, restoring DDP sensitivity, and eliciting robust antitumor immune activation. The synergy among these mechanisms

leads to substantial suppression of drug-resistant tumor growth and outstanding therapeutic efficacy.

3 | Conclusion

In this study, we developed a DDP-doped BP nanomedicine, which effectively reverses chemoresistance by precisely disrupting the adaptive homeostasis of DDP-resistant tumor cells via a piezoelectric mechanism. By facilitating efficient cellular internalization via an endocytic pathway, DDP-BP@PDA bypasses the downregulated drug influx transporters in resistant cells to ensure sufficient intracellular drug accumulation well disrupts the redox equilibrium through piezoelectric catalysis, to weaken their detoxification and antioxidant defense systems. More importantly, by targeting one of the core mechanisms of resistance-enhanced DNA repair, DDP-BP@PDA leverages piezoelectric polarization to enhance the POD-like activity of the Pt single-atom nanozyme, thereby promoting excessive ROS generation. This process triggers pronounced ER stress and suppresses the expression of key DNA repair enzymes, including XPA and XPF. Through these coordinated actions, DDP-BP@PDA dismantles the adaptive homeostasis of DDP-resistant cells, leading to marked suppression of DDP-resistant tumor progression. Overall, this work proposes a conceptually innovative and highly promising therapeutic strategy to overcome chemoresistance by exploiting piezoelectric stimulation to destabilize the adaptive homeostasis of DDP-resistant cells.

4 | Methods

4.1 | Chemicals

BP was purchased from Kunming Black Phosphorus Technology Co., Ltd. (Kunming, China). Dopamine hydrochloride, N-methyl pyrrolidone (NMP, 99%), TMB, MB, DTNB, and GSH were obtained from Aladdin Reagents. DDP was purchased from Med-ChemExpress. Calcein acetoxymethyl ester (Calcein-AM), PI, the JC-1, 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA), and DNA Damage Assay Kit by γ -H2AX Immunofluorescence were obtained from Beyotime Biotechnology Co., Ltd. All chemicals and reagents were used as received without further purification.

4.2 | Characterization

TEM images, HAADF-STEM images, and EDS spectra were obtained using a FEI Tecnai G2 F20 microscope, operated at an acceleration voltage of 200 kV. Spherical aberration-corrected STEM imaging was performed on a JEM ARM 300F microscope at 200 kV. Fourier transform infrared spectroscopy was obtained from a Nicolet iS50 Fourier transform infrared spectrometer (Thermo Scientific, USA). XRD patterns were recorded on a D/tex Ultima TV system using Cu K α radiation ($\lambda = 0.15418$ nm). Raman scattering measurements were conducted with a LabRAM HR Evolution high-resolution confocal Raman microscope, employing a 532 nm laser as the excitation source. The sample thickness was measured using an MFP-D-SA-DV atomic force microscope. XPS analysis was performed using a Kratos Axis Ultra DLD spectrometer, with all elemental spectra calibrated against the C

1s peak at 284.8 eV. Data processing for XANES was conducted using the Athena program [36]. For EXAFS analysis, data analysis was performed with Artemis [37, 38]. Wavelet-transformed k^3 -weighted EXAFS data were analyzed using the Hama Fortran code, with a radial range of 0–6 Å and k -weighting of 0. The kappa-Morlet wavelet with a value of 10 for kappa and 1 for sigma was selected as the mother wavelet to provide the overall distribution [39].

4.3 | Synthesis of BP NSs

BP NSs were synthesized in NMP via ultrasonic liquid-phase exfoliation. Specifically, 80 mg of Bulk BP was finely ground and dispersed in NMP at a concentration of 1 mg mL⁻¹, followed by nitrogen purging for 30 min to remove dissolved oxygen. The mixture underwent ultrasonic treatment at a frequency of 20–25 kHz using a probe ultrasonication for 10 h at a power of 400 W and subsequently centrifuged at 6000 rpm for 10 min to eliminate unexfoliated Bulk BP.

4.4 | Synthesis of DDP-BP@PDA

To synthesize DDP-BP@PDA, the as-prepared BP NSs were repeatedly washed with anhydrous ethanol and redispersed in 18 mL of anhydrous ethanol (1 mg mL⁻¹). The suspension was then combined with DDP (4.5 mg mL⁻¹, 1 mL) and subjected to ultrasonication for 30 min. Subsequently, 180 µL of dopamine hydrochloride aqueous solution (150 mg mL⁻¹) and 450 µL of NaOH aqueous solution (20 mg mL⁻¹) were added, followed by stirring in the dark for 2.5 h. The DDP-BP@PDA was obtained by centrifugation at 9000 rpm for 10 min and washed with water.

4.5 | Piezocatalytic Effect of DDP-BP@PDA on Degradation of MB

The piezocatalytic activity of DDP-BP@PDA under US irradiation (1.0 W·cm⁻², 1.0 MHz, 50% duty cycle) was assessed using MB as a probe. BP@PDA or DDP-BP@PDA (50 µg mL⁻¹) was dispersed in 6 mL of MB solution (5 µg mL⁻¹) and subjected to US under dark conditions for varying durations. The degradation of MB was monitored by recording absorbance changes at 664 nm using UV-vis spectroscopy.

4.6 | POD-Like Activity of DDP-BP@PDA

A 4.8 mg mL⁻¹ TMB working solution was prepared by dissolving 4.8 mg of TMB in 1 mL of dimethyl sulfoxide (DMSO). The POD-like activity of DDP-BP@PDA was evaluated using TMB as a substrate in the presence of H₂O₂. Briefly, DDP-BP@PDA (35 µg mL⁻¹) was added to 6.0 mL of solution containing 240 µL of TMB (4.8 mg mL⁻¹) and 1 mM H₂O₂ to initiate the chromogenic reaction. The absorbance of oxTMB was measured at a wavelength of 652 nm using UV-vis spectroscopy.

4.7 | Steady-State Kinetic Analysis of POD-Like Catalytic Activity

A TMB stock solution was prepared by dissolving 4.8 mg of TMB in 1 mL of dimethyl sulfoxide/ethanol mixed solvent (1:9, v/v), yielding a concentration of 4.8 mg mL⁻¹. The POD-like activity of DDP-BP@PDA was assessed using TMB as the chromogenic substrate in the presence of H₂O₂. In brief, 30 µL of DDP-BP@PDA suspension (2 mg mL⁻¹) was added to an aqueous reaction mixture containing 80 µL of TMB stock solution and H₂O₂ at the indicated concentrations, and the final volume was adjusted to 2.0 mL with ultrapure water. The time-dependent absorbance at 652 nm was recorded every 2 s using a Shimadzu UV-3600 spectrophotometer. After background correction, the initial reaction velocity was determined from the linear portion of the absorbance–time curve. The absorbance change was converted to the concentration of oxidized TMB according to the Beer–Lambert law:

$$A = \epsilon bc$$

where (A) is the absorbance at 652 nm, (b) is the optical path length of 1.0 cm, (ϵ) is the molar extinction coefficient of oxidized TMB (39000 M⁻¹ cm⁻¹), and (c) is the concentration of oxidized TMB. The apparent kinetic parameters were determined by nonlinear fitting of the initial velocities to the Michaelis–Menten equation:

$$V_0 = V_{max} [S] / (K_m + [S])$$

where (V₀) is the initial reaction velocity, (V_{max}) is the maximum reaction velocity, ([S]) denotes the substrate concentration, and (K_m) is the apparent Michaelis constant.

4.8 | Detection of ROS by ESR

For ESR analysis, DDP-BP@PDA (35 µg mL⁻¹) was added to a solution containing H₂O₂ (1 mM) and DMPO (100 mM). Following US irradiation (1.0 W·cm⁻², 1.0 MHz, 50% duty cycle, 3 min), the mixture was collected with a capillary tube and subjected to ESR measurement.

4.9 | Cell Culture

The B16-F10 cell line was purchased from American Type Culture Collection (ATCC). Following the protocol developed by Gottesman [40], the resistant derivatives B16-F10/DDP were selected by culturing parental B16-F10 cells with stepwise increases in DDP for several months. The B16-F10 and B16-F10/DDP cell lines were cultured in RPMI-1640 medium. All the cancer cells were supplemented with 10% (v/v) FBS and 1% (v/v) penicillin/streptomycin. DDP (8 µM) was added to the B16-F10/DDP culture medium to maintain DDP resistance, and the cells were passaged twice to avoid residual DDP bound to the cells before use in experiments. The cancer cells were cultured in a three-gas incubator with 5% CO₂ at 37°C.

4.10 | Bio-TEM Observation

To investigate the interactions between mitochondria and the ER in B16-F10/DDP cells, cells were incubated with DDP-BP@PDA ($20 \mu\text{g mL}^{-1}$) for 4 h, followed by US irradiation in the DDP-BP@PDA+US group (1.0 MHz , 1.0 W cm^{-2} , 50% duty cycle, 2 min). After incubation for 18 h, cells were fixed with 2.5% glutaraldehyde for 5 min, scraped, and collected by centrifugation at 1000 rpm for 3 min. The collected cells were further fixed in glutaraldehyde, and ultrathin sections were prepared for Bio-TEM analysis.

4.11 | In Vitro Cell Viability Assessment

To exclude potential confounding effects of BP@PDA and US, B16-F10/DDP cells were seeded in 96-well plates and exposed to varying concentrations of BP@PDA or different durations of US irradiation. After 24 h of incubation, $10 \mu\text{L}$ of CCK-8 solution was added to each well and incubated for an additional 2 h. Subsequently, $80 \mu\text{L}$ of supernatant was collected, and absorbance was measured at 450 nm.

For therapeutic evaluation, B16-F10/DDP cells were seeded in 96-well plates and cultured for 24 h. After removing the culture medium, DDP-BP@PDA dissolved in complete medium was added at final concentrations of 10, 20, and $40 \mu\text{g mL}^{-1}$. Following 4 h of incubation, cells in the BP@PDA+US and DDP-BP@PDA+US groups were immediately subjected to sonication (1.0 W cm^{-2} , 1.0 MHz , 5 min, 50% duty cycle). The cells were then further incubated for 20 h, and viability was assessed using the CCK-8 assay.

4.12 | In Vitro Live-Dead Staining

B16-F10/DDP cells were seeded in 12-well plates and incubated overnight and divided into the following experimental groups: control (PBS), DDP, DDP-BP@PDA, BP@PDA+US, and DDP-BP@PDA ($20 \mu\text{g mL}^{-1}$) +US (1.0 W cm^{-2} , 1.0 MHz , 2 min, 50% duty cycle). Viable cells were stained with Calcein-AM, while dead cells were labeled with PI. After a 30 min incubation, the cells were washed twice with PBS and imaged using fluorescence microscopy.

4.13 | Intracellular ROS Evaluation

Intracellular ROS generation was assessed using a protocol analogous to the Calcein-AM/PI staining described above, except that cells were pretreated with DCFH-DA (Beyotime Biotechnology). B16-F10/DDP cells were then subjected to US irradiation (1.0 MHz , 1.0 W cm^{-2} , 50% duty cycle, 2 min) and incubated for an additional 30 min. Finally, cells were washed three times with PBS and imaged by CLSM.

4.14 | Mitochondrial Membrane Potential Assessment

B16-F10/DDP cells were seeded in confocal dishes and subjected to the indicated treatments. Following multiple PBS washes, cells were incubated with JC-1 staining solution at 37°C for 20 min. The transition from JC-1 monomers to aggregates indicated a reduction in mitochondrial membrane potential. Fluorescence signals were subsequently visualized using CLSM.

4.15 | Ca^{2+} Signaling Analysis

B16-F10/DDP cells cultured in glass-bottomed dishes were treated with the corresponding drugs and subsequently incubated with Fluo-4 AM (Beyotime Biotechnology) dissolved in PBS for 30 min at 37°C in the dark under 5% CO_2 . Following two PBS washes, cells were imaged by CLSM, and fluorescence intensity was quantified using ImageJ software.

4.16 | Imaging of ER-mitochondria Colocalization

B16-F10/DDP cells were seeded in glass-bottomed culture dishes and divided into the following experimental groups: control (PBS), DDP, DDP-BP@PDA, BP@PDA+US, and DDP-BP@PDA+US ($20 \mu\text{g mL}^{-1}$, 1.0 W cm^{-2} , 1.0 MHz , 2 min, 50% duty cycle). After treatment, cells were washed twice with PBS and incubated with Mito-Tracker Red (Thermo Fisher Scientific) and ER-Tracker Green (Beyotime Biotechnology) at 37°C for 30 min, followed by staining with Hoechst 33342 (Thermo Fisher Scientific) for 10 min. The cells were then rinsed with PBS and imaged using CLSM, and colocalization analysis was performed with ImageJ software.

4.17 | Flow Cytometry Analysis

B16-F10/DDP cells were cultured in 12-well plates and incubated in 2 mL of complete medium for 24 h. The groups included Control (PBS), DDP, DDP-BP@PDA, BP@PDA+US, and DDP-BP@PDA+US ($20 \mu\text{g mL}^{-1}$, 1.0 W cm^{-2} , 1.0 MHz , 2 min, 50% duty cycle). Following treatment, cells were harvested, resuspended in binding buffer, and stained with FITC-Annexin V and PI for 20 min at room temperature. After the addition of fresh binding buffer, apoptosis was quantified by flow cytometry based on fluorescence intensity.

4.18 | Western Blotting Analysis

Cells were lysed in RIPA buffer (Solarbio) supplemented with 1% protease and 1% phosphatase inhibitors for 30 min at 4°C . After centrifugation of the lysates, the protein concentration of each sample was determined. The samples were mixed with an appropriate amount of loading buffer and boiled for 10 min at 95°C , then resolved by SDS-PAGE in a 4–20% polyacrylamide gel and transferred onto PVDF membranes. After blocking with fast blocking western, membranes were incubated with the Phospho-PERK

(1:1,000 dilution, 3179, CST Technology), ERCC4 (1:1,000 dilution, M01993, BOSTER), XPA (1:1,000 dilution, AF5336, Beyotime), ATF-4 (1:1,000 dilution, 11815, CST Technology), CTR1 (1:1,000 dilution, 13086, CST Technology), CHOP (1:1,000 dilution, 2895, CST Technology), Beta Tubulin (1:50,000 dilution, 66240, Proteintech) or GAPDH (1:50,000 dilution, 60004, Proteintech) antibody for 12 h at 4°C, followed by incubation with secondary antibodies. Bands were visualized using a chemiluminescence imager.

4.19 | Immunofluorescence Detection of XPF

B16-F10/DDP cells were exposed to the different treatments for 18 h. Cells were subsequently fixed with 4% paraformaldehyde for 15 min at room temperature, permeabilized with 0.5% Triton X-100 for 20 min, and blocked with 5% bovine serum albumin in PBS for 1 h. They were then incubated with the primary antibody anti-ERCC4 (1:100, OTI2D4, Boste) for 1 h at room temperature, followed by incubation with Alexa Fluor 488-conjugated goat anti-mouse IgG (H+L) (1:200, A32723TR, Thermo Fisher Scientific) for 1 h. The cytoskeleton was counterstained with F-actin for 30 min. Fluorescence imaging was performed using CLSM.

4.20 | mRNA Sequencing and Analysis

Following culture of two groups of cells subjected to different treatments, total RNA was extracted using the TRIzol method. RNA samples that passed quality control (RIN > 9.0) were used for library preparation and sequencing on the Illumina HiSeq platform. After quality control and filtering of the raw sequencing data obtained, gene expression quantification and differential analysis were performed using DESeq2, with the criteria for screening differentially expressed genes set as $|\log_2FC| > 1$ and adj. p -value < 0.05.

4.21 | In Vivo Biosafety Assessment

C57BL/6 mice were purchased from SPF (Beijing) Biotechnology Co., Ltd. All animal protocols were approved by the Animal Care and Use Committee of Beijing Institute of Nanoenergy and Nanosystems, Chinese Academy of Sciences. (Approval Number: 2025008LD). Eight-week-old female C57BL/6 mice (~20 g) were randomly assigned to three groups and intravenously administered DDP-BP@PDA dispersed in PBS at doses of 0, 20, or 50 mg kg⁻¹. Throughout the 14-day observation period, health status, behavioral activity, and body weight were monitored. At the end of the study, blood routine and blood biochemical indices were analyzed. Mice were euthanized via painless cervical dislocation, and major organs (heart, liver, spleen, lungs, and kidneys) were harvested for histopathological analysis.

4.22 | In Vivo Therapeutic Effects

A tumor-bearing mouse model was established via subcutaneous injection of B16-F10/DDP melanoma cells. Once tumor volumes reached approximately 50 mm³, mice were randomly assigned to five groups ($n = 5$): (i) Control (PBS), (ii) DDP, (iii) DDP-BP@PDA, (iv) BP@PDA+US, and (v) DDP-BP@PDA+US (1.0 W

cm⁻², 1.0 MHz, 10 min, 50% duty cycle). BP@PDA and DDP-BP@PDA were administered at 10 mg kg⁻¹, with three treatments delivered over 13 days. Tumor volume and body weight were recorded every two days throughout the experimental period. At study completion, mice were euthanized, and tumors along with relevant tissues were harvested for further analysis.

Freshly dissected tumor tissues were fixed in 4% paraformaldehyde (PFA), dehydrated, embedded in paraffin, and sectioned. H&E staining was performed for histological examination. Apoptotic cells were detected using a TUNEL assay kit. Immunofluorescence staining was conducted to assess the expression of the following markers: Ki67, ATF4, CD4, and CD8. All fluorescent images were acquired using a fluorescence microscope.

4.23 | Statistical Analysis

All data were presented as means ± SD and analyzed using GraphPad Prism 8.0. The significance of the data was evaluated according to the one-way analysis of variance (ANOVA) test or two-way ANOVA. * p < 0.05, ** p < 0.01, *** p < 0.001, and **** p < 0.0001. ns, not significant.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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