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*Review*

# DNA Damage Repair Pathways and Targeted Therapy for Doxorubicin-Resistant Breast Cancer

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**Abstract**

Breast cancer, characterized by distinctive epidemiological patterns and substantial heterogeneity, continues to be among the leading causes of cancer-related mortality in women. As breast tumors progressively acquire resistance to doxorubicin (DOX), DNA damage repair (DDR) pathways are recognized as key determinants of both DOX efficacy and the onset of resistance. Targeting DDR mechanisms in breast cancer patients with specific repair deficiencies offers the potential for personalized therapeutic approaches. This review first discusses the pivotal roles of five major DNA repair pathways (homologous recombination, nonhomologous end-joining, base excision repair, nucleotide excision repair, and mismatch repair) in the development of DOX resistance. This review aims to establish a theoretical framework and reference for future studies on DDR mechanisms in DOX-resistant breast cancer to advance intervention strategies for resistant breast tumors and to promote further research in this area.

**Keywords:** breast neoplasms; drug resistance; neoplasm; doxorubicin; DNA repair; molecular targeted therapy

## 1. Introduction

Breast cancer is characterized by distinctive epidemiological patterns and marked heterogeneity and remains one of the leading causes of cancer-related mortality in women [1]. Epidemiological data indicate that the annual rate of increase in the incidence of breast cancer among women younger than 50 years (1.4%) is significantly greater than that among women aged 50 years and older (0.7%) and that the disparity in growth rates is even more pronounced in white women [2]. The International Agency for Research on Cancer (IARC) projects that by 2040, the global annual number of newly diagnosed breast cancer cases will exceed 3 million [3]. In recent years, research has increasingly focused on the combination of conventional doxorubicin (DOX) therapy with molecularly targeted interventions against DNA repair or the optimization of treatment sequences. Advances in the "targeted and precise" treatment of breast cancer have significantly reshaped clinical practice. For patients who harbour *BRCA1/2* (BRCA1 DNA repair associated/ BRCA2 DNA repair associated) mutations and those who exhibit homologous recombination deficiency (HRD), Poly (ADP–ribose) polymerase (PARP) inhibitors have emerged as a key class of targeted therapy, as they have demonstrated competitive efficacy in both advanced/metastatic settings, and in some cases, early-stage disease [4]. In p53-deficient breast cancer cell lines, PARP inhibition enhances DOX-induced cytotoxicity, which suggests that impairment in DNA repair processes may underlie increased chemosensitivity [5,6]. Antibody–drug conjugates (ADCs), such as Enhertu, Trodelvy, and the recently highlighted Datroway, selectively deliver cytotoxic payloads to cancer cells, expanding the population of "targetable" patients and offering novel alternative or combinatorial strategies to overcome DOX resistance [7]. However, evidence remains limited regarding whether DNA damage repair (DDR) pathway inhibitors can reverse DOX resistance driven by enhanced DNA repair mechanisms. Endocrine therapy combined with CDK4/6 inhibitors, as well as immune checkpoint blockade in specific subtypes, has further reshaped therapeutic options and renders the timing, combination, or substitution of DOX increasingly dependent on tumor molecular profiling and individualized clinical decision-making [8].

DOX is an anthracycline antibiotic originally isolated from a mutant strain of *Streptomyces peucetius* subsp. caesius (ATCC 27952) [9]. The drug and its derivatives were patented by Farmitalia Carlo Erba SpA in 1971 [10,11]. According to the ClinicalTrials.gov registry (https://clinicaltrials.gov), as of February 2025, approximately 1112 clinical trials involving DOX have been registered worldwide. As a prototypical anthracycline, DOX remains a cornerstone of adjuvant, neoadjuvant, and metastatic breast cancer therapy, as this drug markedly improves both overall survival and disease-free survival in long-term clinical practice. Al-

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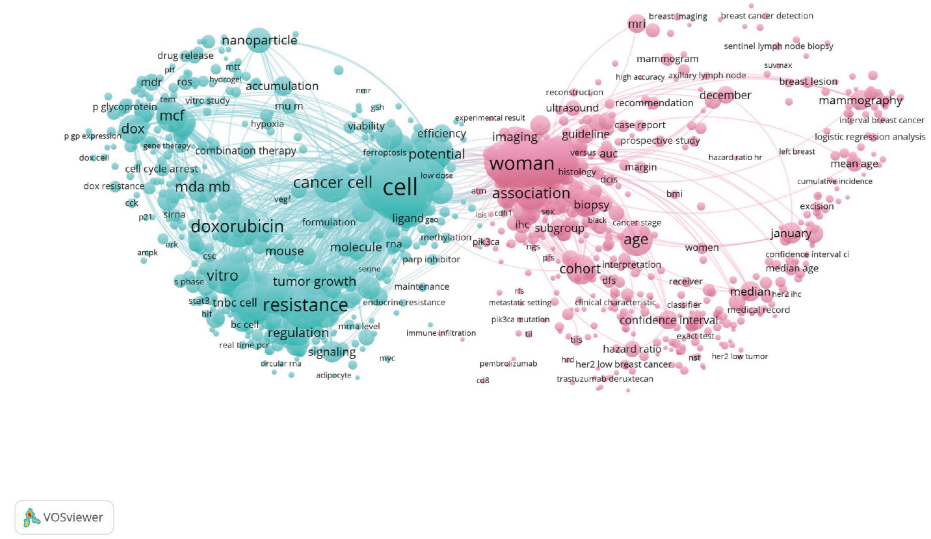


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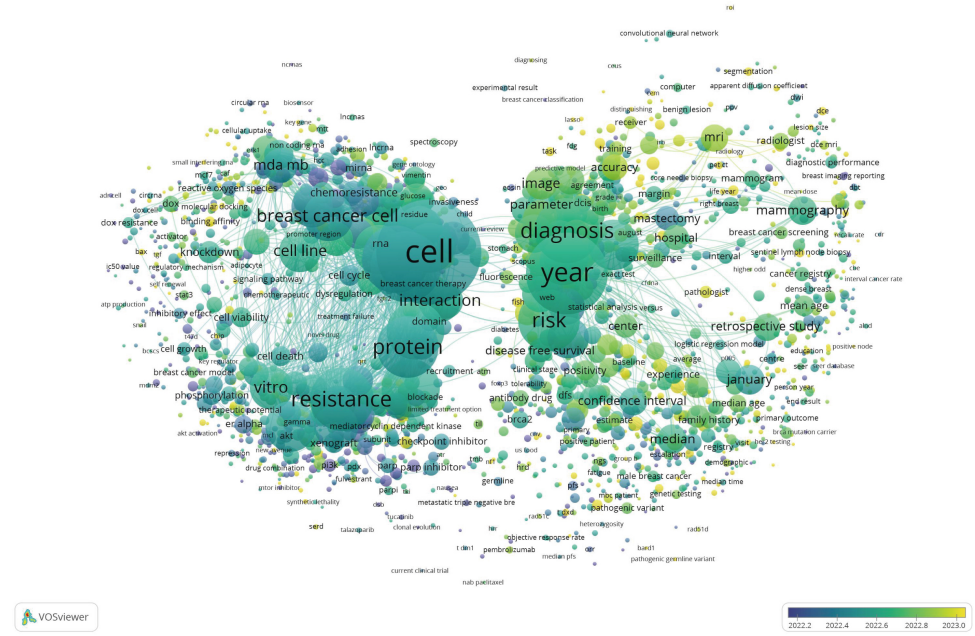


**Fig. 1. Bibliometric keyword co-occurrence analyses of recent literature on DOX resistance in breast cancer.** The literature published during the most recent five-year period was retrieved from the Web of Science database and exported in "Full Record" plain-text (.txt) format. Visual maps were generated in VOSviewer (version 1.6.20) using a minimum keyword occurrence threshold of 10 and were clustered according to node parameters. (A) Network map produced for the search terms "DOX resistance" AND "breast cancer" (n = 7679 records). (B) Network map produced for the search terms "DOX resistance" AND "breast cancer" AND "DDR" (n = 6556 records). In both panels, node size corresponds to keyword frequency, connecting lines indicate keyword co-occurrence relationships (the edge weight reflects co-occurrence strength), and different colours represent thematic clusters identified algorithmically by VOSviewer. No restrictions were applied to the document type, and no additional screening, data processing, or visualization software was used. DOX, doxorubicin; DDR, DNA damage repair. The figure was created using VOSviewer (version 1.6.20, Nees Jan van Eck and Ludo Waltman (Centre for Science and Technology Studies (CWTS) at Leiden University), Leiden, South Holland, The Netherlands). Other figures were created using Adobe Illustrator 2022 (Adobe Inc., San Jose, CA, USA).

though rapid advances in molecular stratification and targeted therapies have rendered DOX no longer the default first-line option in certain breast cancer subtypes, it continues to play a central role in curable early-stage disease, locally advanced cases, and patients who lack effective targeted treatments [12–14].

The antitumor effects of DOX in breast cancer primarily involve its intercalation into double-stranded DNA, inhibition of topoisomerase II (Topo II, a type II DNA topoisomerase that modulates DNA topology by generating transient double-strand breaks (DSBs)), and the consequent induction of DNA damage that triggers tumor cell apoptosis [15]. Despite its considerable clinical efficacy, the use of DOX is limited by intrinsic and acquired resistance. Although triple-negative breast cancer (TNBC) is relatively more sensitive to DOX than are other subtypes, treatment failure due to resistance still affects approximately 30–50% of patients [16]. Aberrant upregulation of DDR pathways is a central mechanism of DOX resistance, as tumor cells repair DOX-induced DNA lesions through increased DNA repair activity, which promotes the development of drug resistance [17,18]. The upregulation of drug efflux pumps, particularly P-glycoprotein (P-gp/ABCB1), ABCG2, and ABCC1, reduces the intracellular accumulation of DOX and represents one of the central mechanisms underlying breast cancer chemoresistance [19]. Tumor cells further evade immune clearance and apoptosis by enhancing the DDR to counteract Topo II inhibition and ROS–induced DNA lesions. Additional factors that attenuate DOX cytotoxicity include the following: decreased expression or functional alterations of Topo II, activation of antiapoptotic pathways such as those mediated by BCL2 apoptosis regulator (BCL-2), Nuclear Factor kappa-B (NF-$\kappa$B), and signal transducer and activator of transcription 3 (STAT3), epithelial–mesenchymal transition (EMT), and enrichment of cancer stem cell traits, autophagy, and reversible senescence, as well as tumor microenvironmental changes, including hypoxia, immune modulation, and extracellular matrix remodelling [20]. Exosome-mediated transfer of resistance phenotypes and epigenetic regulation by noncoding RNAs have also emerged as critical drivers of DOX resistance in recent studies. In the context of these multilayered mechanisms, recent preclinical and translational studies have explored combination strategies, such as the use of PARP, DNA-PK, or ataxia telangiectasia and Rad3-related (ATR) inhibitors, efflux pump modulators, BCL-2 or autophagy inhibitors, and novel drug delivery systems, to increase DOX efficacy. However, evidence remains limited regarding whether DDR pathway inhibitors can reverse DOX resistance driven by enhanced DNA repair mechanisms.

This review describes how DNA repair pathways, homologous recombination (HR), nonhomologous end joining (NHEJ), base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR) contribute to resistance to DOX in breast cancer and critically examines key genes, signalling networks, and their clinical implications [21–23]. This study also provides a detailed evaluation of strategies to overcome resistance to DNA damage induced by DOX in breast cancer cells, combined targeted therapies, noncoding RNA (ncRNA)-mediated sensitization approaches, and interventions with natural bioactive compounds (NPs), with an aim to provide a theoretical foundation and practical reference for the development of antiresistance interventions and to advance research in this field [24,25].

## 2. Bibliometric Analysis of the Past Five Years

The use of VOSviewer (bibliometric mapping software, version 1.6.20, Centre for Science and Technology Studies, Leiden University, Leiden, the Netherlands) [26] to analyse relevant literature from the past five years revealed that research on DOX resistance has evolved from early studies focused on single-cell resistance mechanisms to a broader spectrum that includes nanocarrier-based delivery and ncRNA–mediated regulation, clinical cohort and radiomic (quantitative imaging feature extraction) studies, and integrative multiomics artificial intelligence-based approaches. In 2018–2019, keywords such as “cell viability” and “knockdown” were predominant, reflecting mechanistic investigations into how DOX, through the inhibition of Topo II, induces tumor cell apoptosis, cell cycle arrest, and activation of the DDR and repair processes. From 2020 to 2021, terms such as “nanoparticle”, “liposome”, and microRNA (miRNA) and long noncoding RNA (lncRNA) became markedly more prominent, which indicates that nanoparticle-based delivery strategies and RNA-mediated regulation of the DDR, encompassing lesion detection, signalling, and repair, were needed. Multiple miRNAs and lncRNAs have been reported to modulate resistance by targeting DNA repair genes. Concurrently, the frequent occurrence of “retrospective study” and “disease-free survival” signals the growing application of retrospective cohort analyses for prognostic evaluation. In 2022–2023, an increasing trend was observed towards the integration of radiomics and deep learning with genomics, transcriptomics, metabolomics, and epigenomics as well as combinations with artificial intelligence methods, to enable earlier detection of resistance, risk stratification, and extraction of DDR-related imaging features. In conclusion, literature within the past five years shows a shift from predominantly *in vitro* or *in vivo* mechanistic studies towards a more balanced emphasis on nanomedicine, ncRNA regulation, combined imaging/AI and multiomics approaches, and clinical cohort research (Fig. 1A,B).

The core mechanisms underlying DOX resistance in breast cancer have been elucidated primarily at the cellular level in models using MDA-MB-231 and MCF-7 cells. These mechanisms primarily involve antiapoptotic

signalling and the transcriptional and posttranscriptional regulation of genes and proteins, which enhance the proliferative capacity of resistant cells. To overcome resistance, current research has focused on nanodelivery platforms and combination therapeutics. Nanoparticle-based drug delivery systems can improve the pharmacokinetic profile of DOX, increase tumor selectivity, and reduce systemic toxicity and are therefore considered among the most promising approaches for clinical translation. lncRNAs have emerged as key regulators of resistance-associated gene expression, whereas extracellular vesicles serve as carriers of lncRNAs or miRNAs that enable intercellular transfer of resistance phenotypes. With the rapid accumulation of multiomics datasets, systems biology and machine learning approaches are accelerating the identification of resistance-related biomarkers and regulatory networks. This offers new strategies for clinical resistance stratification, prediction of the therapeutic response to DOX, and the development of precision treatment approaches.

## 3. DSB Repair Pathways

DSBs are among the most deleterious forms of DNA damage and are principally repaired via two pathways: HR and NHEJ. The expression levels of key HR factors are significantly associated with DOX resistance in breast cancer cells [27]. Dysregulation of DSB repair commonly manifests as an imbalance in these pathways: aberrant expression or functional impairment of critical genes not only compromises the high-fidelity repair mediated by HR but also drives hyperactivation of NHEJ, which promotes DOX resistance and supports breast cancer cell proliferation.

### *3.1 HR-Mediated Mechanisms of DOX Resistance in Breast Cancer*

The HR pathway comprises three principal subpathways—DSB repair, synthesis-dependent strand annealing (SDSA), and break-induced replication (BIR) [28]. HR is a high-fidelity, template-dependent mechanism that uses sister chromatids to accurately repair DSBs [29]. Key HR proteins include RAD51 recombinase (RAD51), RAD52 DNA repair protein (RAD52), DNA-dependent ATPase RAD54 (RAD54), replication protein A (RPA), RAD51 paralog B (RAD51B), RAD51 paralog C (RAD51C), RAD51 paralog D (RAD51D), X-ray repair cross complementing 2 (XRCC2), and X-ray repair cross complementing 3 (XRCC3), and the breast cancer susceptibility proteins BRCA1 and BRCA2. The overexpression of RAD51 and BRCA1 enhances HR-mediated repair, promotes breast cancer cell survival, and alters cell cycle control, which reduces DOX-induced cell death and contributes to chemoresistance [30,31]. For example, Shan Wang *et al.* [32] reported that E2F transcription factor 8 (E2F8) upregulates RAD51 in breast cancer cells, which in turn promotes HR activity and contributes to DOX resistance. epithelial membrane protein 3 (EMP3) functions as a tumor inhibitor in breast cancer by inhibiting DNA replication, impairing HR, reducing tumor cell stem-like properties, and inhibiting oncogenic signalling [33]. For example, Kailing Zhou *et al.* [34] demonstrated that EMP3 downregulation is associated with decreased expression of the cell cycle regulator p21, upregulation of S–phase–associated factors, reduced phosphorylated histone H2A.X ($\gamma$-H2AX) levels, and increased BRCA1 and RAD51 expression, which are all changes that are consistent with increased DNA repair capacity and markedly increased tolerance to DOX. Other studies demonstrated that EMP3 loss can activate the AKT–mTOR signalling axis to inhibit autophagy and upregulate the expression of the $N^6$-methyladenosine (m6A) reader YTH N6-methyladenosine RNA binding protein C1 (YTHDC1), which increases DNA repair competence and DOX resistance [34]. YTHDC1, which acts downstream of EMP3, mediates EMP3-related regulation of HR; experimentally, either EMP3 restoration or YTHDC1 suppression increases the sensitivity of breast cancer cells to DOX [35]. Conversely, YTH N6-methyladenosine RNA binding protein F1 (YTHDF1) acts as an oncogenic m6A reader in breast cancer to promote tumorigenesis and chemoresistance by facilitating DNA replication and accelerating HR-dependent repair (Fig. 2) [36].

Overexpression of RAD51 and *BRCA1/2* enhances the accuracy of DSB repair and reduces DOX-induced cell death. Elevated levels of E2F8 and CENPL similarly promote resistance by upregulating RAD51 expression or increasing DNA repair capacity. Downregulation of EMP3 leads to decreased p21 expression, increased S-phase–associated factor expression, reduced $\gamma$-H2AX expression, and concomitant upregulation of BRCA1 and RAD51 expression, which further increases HR-mediated repair. Low EMP3 expression also activates the AKT–mTOR signalling pathway and increases the expression of the m6A reader YTHDC1, which increases DNA repair and facilitates resistance acquisition. YTHDF1 promotes DOX tolerance by upregulating the expression of E2F8 and key HR repair proteins, including BRCA1, RAD51, BRCA2, BARD1, and PALB2, accelerating HR-mediated DSB repair. The RAD51/BRCA1/2 axis, E2F8, CENPL, EMP3, and their downstream regulators YTHDC1, YTHDF1, and the AkT–mTOR pathway represent potential predictors of DOX sensitivity and promising therapeutic targets for reversing resistance.

The inhibition of RAD51 prevents its binding to single-stranded DNA (ssDNA) and blocks nucleofilament formation, disrupting a central step of HR and preventing the repair of DSBs. Suppression of the assembly of HR complexes involving BRCA1, BRCA2, or PALB2 diminishes template-dependent repair capacity and drives tumor cells into a state resembling “functional HR deficiency”. Likewise, inhibition of YTHDF1 reduces HR repair capacity by preventing its regulatory effect on E2F8, which

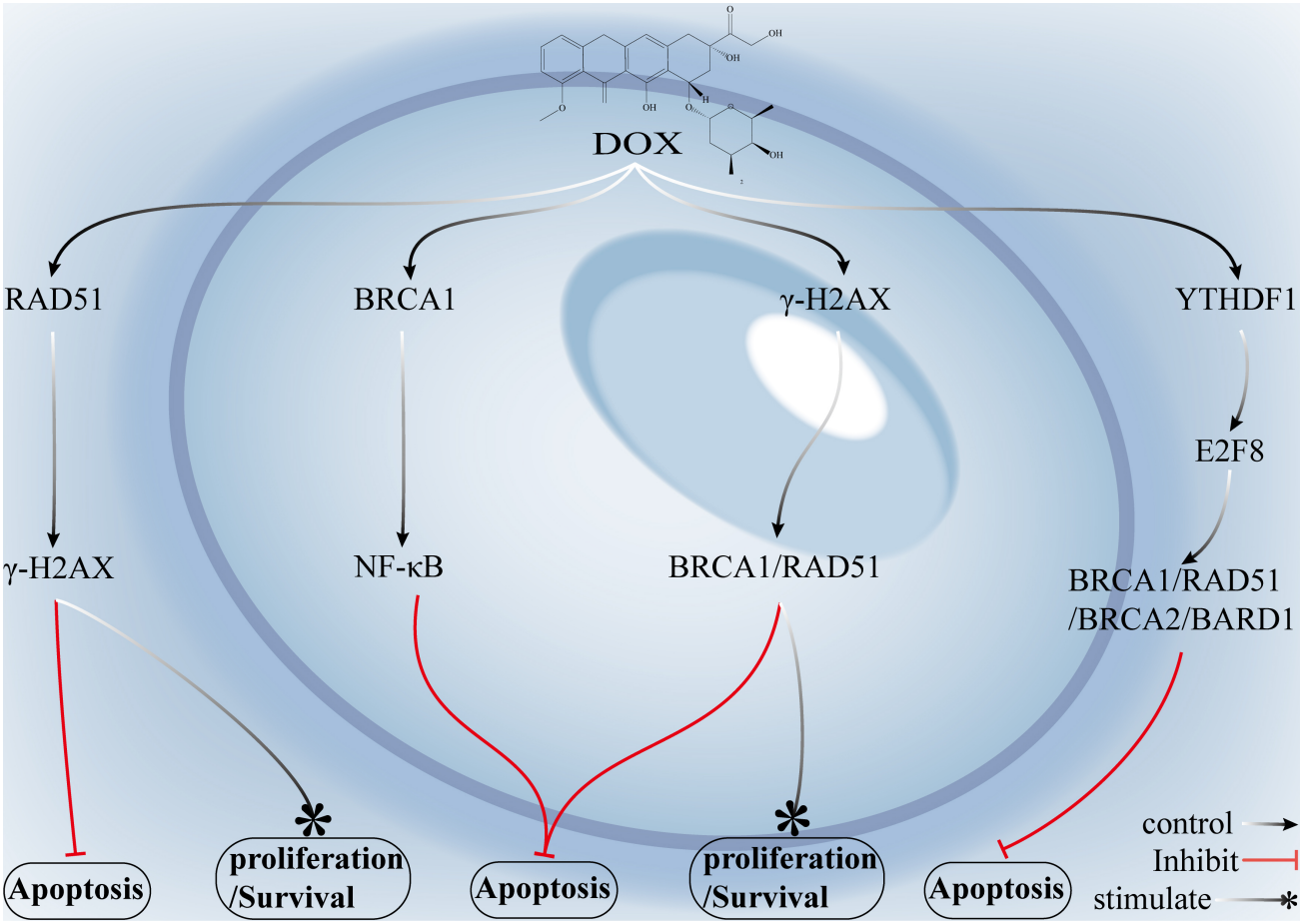


**Fig. 2. Mechanisms by which key genes in the HR pathway and associated signalling networks mediate DOX resistance in breast cancer.** DOX induces DSBs primarily by inhibition of topoisomerase II (Topo II), which subsequently triggers the phosphorylation of γ-H2AX and activates the HR repair pathway. The γ-H2AX foci formed at damage sites provide a platform for the recruitment of BRCA1 and upstream RAD51-loading factors. Through the combined effects of genomic instability and DNA damage–induced apoptosis, this signalling axis paradoxically contributes to enhanced DOX resistance in breast cancer cells. BRCA1 can also activate NF-κB under conditions of DNA damage, further promoting cell proliferation and resistance to DOX. YTHDF1 stabilizes E2F8 mRNA and upregulates the expression of key HR components, including BRCA1, BRCA2, RAD51, BARD1, and PALB2, which increases HR repair activity and markedly reduces DOX-induced apoptosis. Phosphorylated histone H2A.X (γ-H2AX): A phosphorylated form of the H2A histone variant that marks DNA DSBs. BRCA1 DNA repair associated (BRCA1): A tumor suppressor gene essential for HR-mediated DNA repair. BRCA1 associated RING domain 1 (BARD1): The obligatory binding partner of BRCA1 that forms a BRCA1–BARD1 heterodimer with E3 ubiquitin ligase activity. Partner and localizer of BRCA2 (PALB2): A bridging protein that links BRCA1 to BRCA2 and directly promotes RAD51 activity and nucleoprotein filament formation. Nuclear Factor kappa-B (NF-κB): A family of inflammation- and survival-associated transcription factors. YTH N6-methyladenosine RNA binding protein F1 (YTHDF1): An m6A "reader" protein that enhances translation or stabilizes m6A-modified mRNAs. E2F transcription factor 8 (E2F8): A member of the E2F transcription factor family involved in cell cycle control and transcriptional regulation. HR, homologous recombination; DSBs, double-strand breaks; RAD51, RAD51 recombinase.

in turn governs the expression of BRCA1, BRCA2, and RAD51. Activation of the AkT–mTOR signalling axis enhances DNA repair and cell survival, and blockade of this pathway using AkT or mTOR inhibitors indirectly downregulates HR-related gene expression, which restores the cytotoxic effects of doxorubicin.

### *3.2 NHEJ-Mediated Mechanisms of DOX Resistance in Breast Cancer*

In canonical NHEJ, the Ku heterodimer (Ku70/Ku80) serves as the core DNA end recognition factor that rapidly binds to DNA double-strand break ends and recruits downstream repair proteins to initiate end joining [37,38]. The catalytic subunit DNA-dependent protein kinase catalytic subunit (DNA-PKcs) associates with the Ku complex and

phosphorylates downstream effectors to promote DSB repair. Reduced Ku80 expression impairs NHEJ activity and attenuates the DNA repair capacity of otherwise resistant tumor cells, sensitizing them to DOX. Conversely, high Ku70/Ku80 expression facilitates rapid end stabilization, the recruitment of downstream factors, and efficient NHEJ, which enables tumor cells to evade apoptosis or necrosis [39,40]. For example, Min-Gu Lee *et al*. [41] reported that the upregulation of MDR1 enhances DOX efflux and decreases intracellular drug accumulation, contributing to chemoresistance. Cotreatment with DOX and the natural product arctigenin (ATG) substantially increases $\gamma$-H2AX phosphorylation while downregulating the DNA repair proteins RAD51 and Ku80, leading to DNA damage accumulation, diminished repair, and tumor cell death. DNA-PK (a serine/threonine kinase) cooperates with Ku70/Ku80, XRCC4, and DNA ligase IV to mediate the final ligation step of NHEJ. The phosphorylation of downstream substrates by DNA-PKcs facilitates DSB resolution, while functional impairment of DNA-PKcs disrupts NHEJ and can reduce DOX resistance in breast cancer cells [42,43]. For example, Steffie Revia *et al*. [44] demonstrated that DOX-induced DNA damage activates DNA-PK and promotes cell survival and resistance through NHEJ. The DNA-PK inhibitor peposertib directly inhibits DNA-PK activity and effectively blocks NHEJ. The inhibition of NHEJ prevents the repair of DOX-induced DSBs, resulting in the accumulation of damage that activates the ataxia telangiectasia mutated (ATM) signalling cascade and the downstream p53 pathway. ATM activation increases phosphorylated KAP1 (p-KAP1) and phosphorylated p53 (p-p53), induces transcription of the p53 target p21, and triggers cell cycle arrest and apoptosis mechanisms that can overcome DOX resistance in breast cancer (Fig. 3).

High expression of Ku70/Ku80 and DNA-PK enhances end-break stabilization and repair efficiency, and thus they constitute key molecular nodes that promote DOX resistance. Suppression or functional impairment of these factors markedly decreases NHEJ efficiency and increases cellular sensitivity to DOX. MDR1 further reinforces the resistant phenotype by increasing DOX efflux and reducing drug accumulation in the nucleus. Treatment with ATG or the DNA-PK inhibitor peposertib downregulates the expression of repair proteins such as Ku80 and RAD51, which blocks NHEJ repair, promotes the accumulation of DOX-induced DNA damage, and subsequently activates the ATM–p53–p21 axis to trigger cell cycle arrest and apoptosis. The inhibition of the Ku70/Ku80–DNA-PK–mediated NHEJ pathway, together with overcoming MDR1-driven drug efflux, has been consistently shown in extensive preclinical and early clinical studies to potentiate DOX cytotoxicity and reverse resistance. Peposertib is already under evaluation in phase I and combination trials. However, challenges remain, including toxicity to normal tissues due to a narrow therapeutic window and compensatory and heterogeneous repair pathway activation [45,46]. Improvements in safety will require biomarker-guided patient stratification, short-pulse or precisely timed combination dosing, optimized drug administration and delivery strategies, and the development of tumor-targeted delivery systems or low-toxicity efflux inhibitors.

### *3.3 BER-Mediated Mechanisms of DOX Resistance in Breast Cancer*

The BER pathway is a major DNA repair mechanism responsible for the removal of oxidative, alkylation, and base loss (depurination/depyrimidination) lesions that do not typically grossly distort the DNA helix. BER is generally initiated by a family of DNA glycosylases that excise damaged bases and generate apurinic/apyrimidinic (AP) sites [47–49]. Apurinic/apyrimidinic endonuclease 1 (APE1) contains two functional domains: a C-terminal domain that mediates canonical BER activity and an N-terminal domain that performs redox (reduction–oxidation) regulatory functions [50]. APE1 possesses intrinsic redox enzyme activity. This activity increases under hypoxic conditions and contributes to tumor cell resistance to DOX. The inhibition of the redox function of APE1 can markedly increase the cytotoxic efficacy of DOX [51,52]. For example, Ísis Salviano Soares de Amorim *et al*. [52] reported that under hypoxia, treatment with the APE1 inhibitor APX2009 in combination with DOX significantly increases apoptosis and caspase-3/7 activity in MDA-MB-231 cells. This combination also promotes intracellular DOX accumulation. These findings further demonstrate that caspase-3 is the key mediator of the cytotoxic effects induced by this combination treatment.

The overexpression of flap endonuclease 1 (FEN1) has been reported to accelerate BER-mediated resolution of DOX-induced abasic sites and single-strand breaks (SSBs); this reduces DNA damage accumulation and allows breast tumor cells to clear lethal lesions rapidly and evade DOX cytotoxicity, which ultimately promotes chemoresistance [53–55]. For example, Xiao Lu *et al*. [56] reported that the transcription factor Yin Yang 1 (YY1) normally activates miR-140 expression; in DOX-resistant breast cancer cells, the regulation of miR-140 by YY1 is weakened, leading to the downregulation of miR-140 expression, the consequent upregulation of FEN1 expression, increased DNA repair efficiency, and the development of resistance.

Nei-like 2 (NEIL2), a DNA glycosylase central to the BER pathway, is upregulated in breast cancer stem cells and confers protection through two synergistic mechanisms: (1) direct excision of DOX-induced base lesions and SSBs and (2) mitigation of secondary DNA damage that arises from reactive oxygen species (ROS) and contributes to DOX resistance in breast cancer [57–59]. For example, Banerjee *et al*. [58] demonstrated that by inhibiting p300-mediated acetylation (p300 is a histone acetyltransferase), DOX induces NEIL2 expression at both the transcriptional

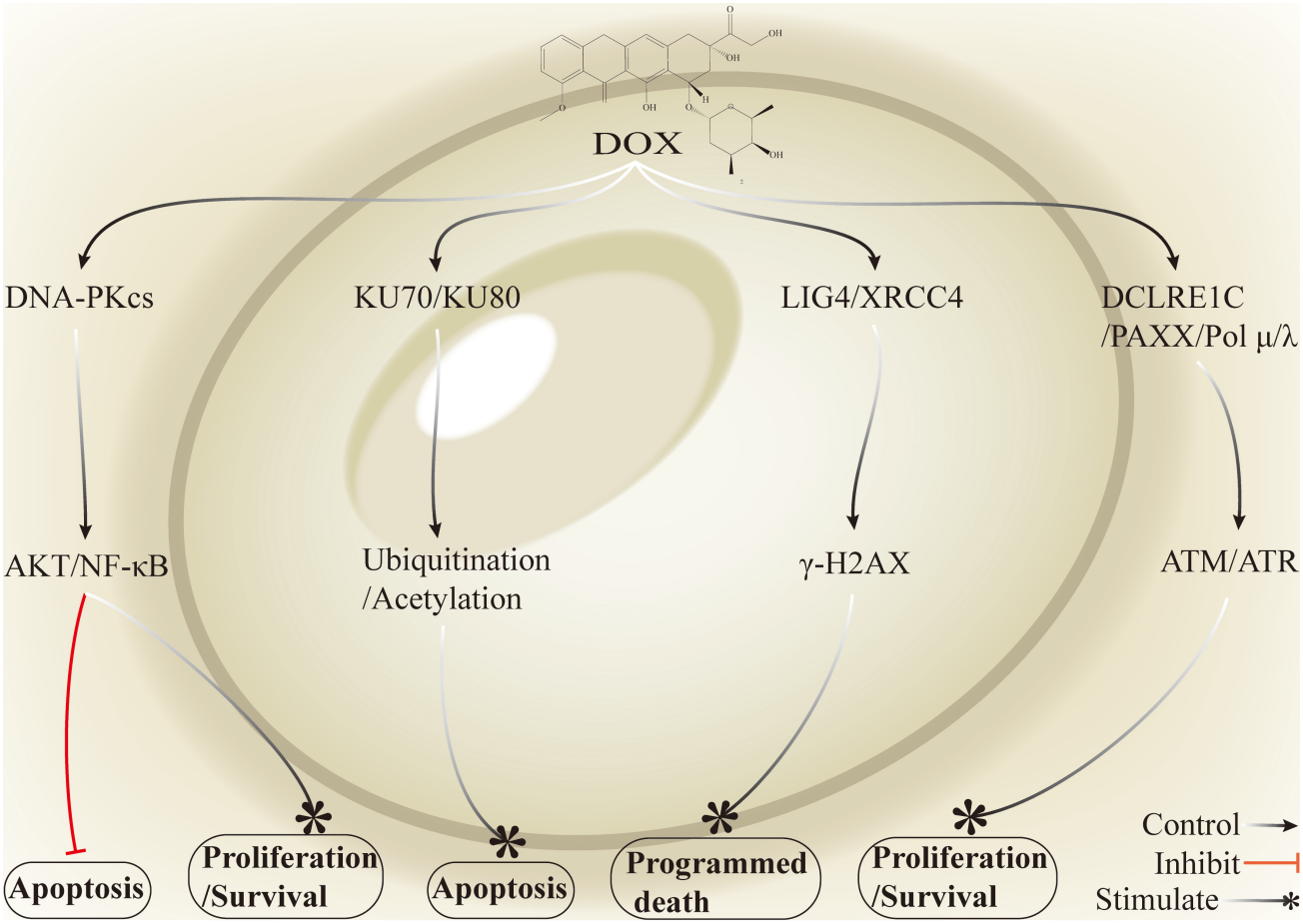


**Fig. 3. Mechanisms by which key genes in the NHEJ pathway and associated signalling networks mediate DOX resistance in breast cancer.** Activation of DNA-PKcs promotes the phosphorylation and activation of AKT and interactions with the NF-$\kappa$B signalling cascade, increasing cell survival and contributing to DOX tolerance. Ku70 and Ku80 regulate end binding and NHEJ efficiency by modulating Ku–protein interactions and complex stability. Acetylation of Ku70 disrupts its association with the pro-apoptotic factor Bax, resulting in Bax release and the induction of apoptosis. Impaired function of the XRCC4–LIG4 complex hinders the completion of DSB repair, which leads to the persistent accumulation of $\gamma$-H2AX foci and triggers cell cycle arrest or programmed cell death. Loss or dysfunction of DCLRE1C, PAXX, and Pol $\mu$/Pol $\lambda$ amplifies signals derived from unrepaired or misrepaired DNA ends, activates the ATM/ATR checkpoint, and typically results in growth inhibition or cell death. These repair defects can also increase genomic instability, indirectly fuelling tumor evolution and intratumoral heterogeneity. LIG4/XRCC4: DNA ligase IV forms a terminal-ligation complex with XRCC4 to complete NHEJ-mediated DNA end joining. DNA cross-link repair 1C (DCLRE1C): A nuclease with endonuclease/exonuclease activity involved in DNA end processing. PAXX non-homologous end joining factor (PAXX): A paralogue of XRCC4/XLF that stabilizes the NHEJ machinery through interaction with Ku. Pol $\mu$/Pol $\lambda$: Specialized DNA polymerases that mediate variable end-filling and template-dependent or template-independent synthesis, which facilitates the ligation of complex DNA ends during NHEJ. NHEJ, nonhomologous end joining; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related; DNA-PKcs, DNA-dependent protein kinase catalytic subunit.

and translational levels, enabling cells to withstand DNA damage and ROS-induced stress and acquire chemoresistance. Furthermore, studies have demonstrated that the survival and DOX resistance of breast cancer stem cells are enhanced through the regulation of redox homeostasis [58] (Fig. 4).

APE1 not only participates in the DNA BER pathway but also markedly upregulates redox activity in the hypoxic tumor microenvironment, where it can inhibit caspase-3/7–mediated apoptosis and reduce intracellular DOX accumulation, contributing to the development of a drug-resistant phenotype in breast cancer cells. FEN1 overexpression enhances BER-mediated repair of DOX-induced base lesions and strand breaks, decreases DNA damage accumulation and enables tumor cells to rapidly eliminate lethal lesions. NEIL2 is upregulated in breast cancer stem cells and promotes cell survival and drug resistance by removing DOX-induced DNA damage and suppressing ROS-mediated sec-

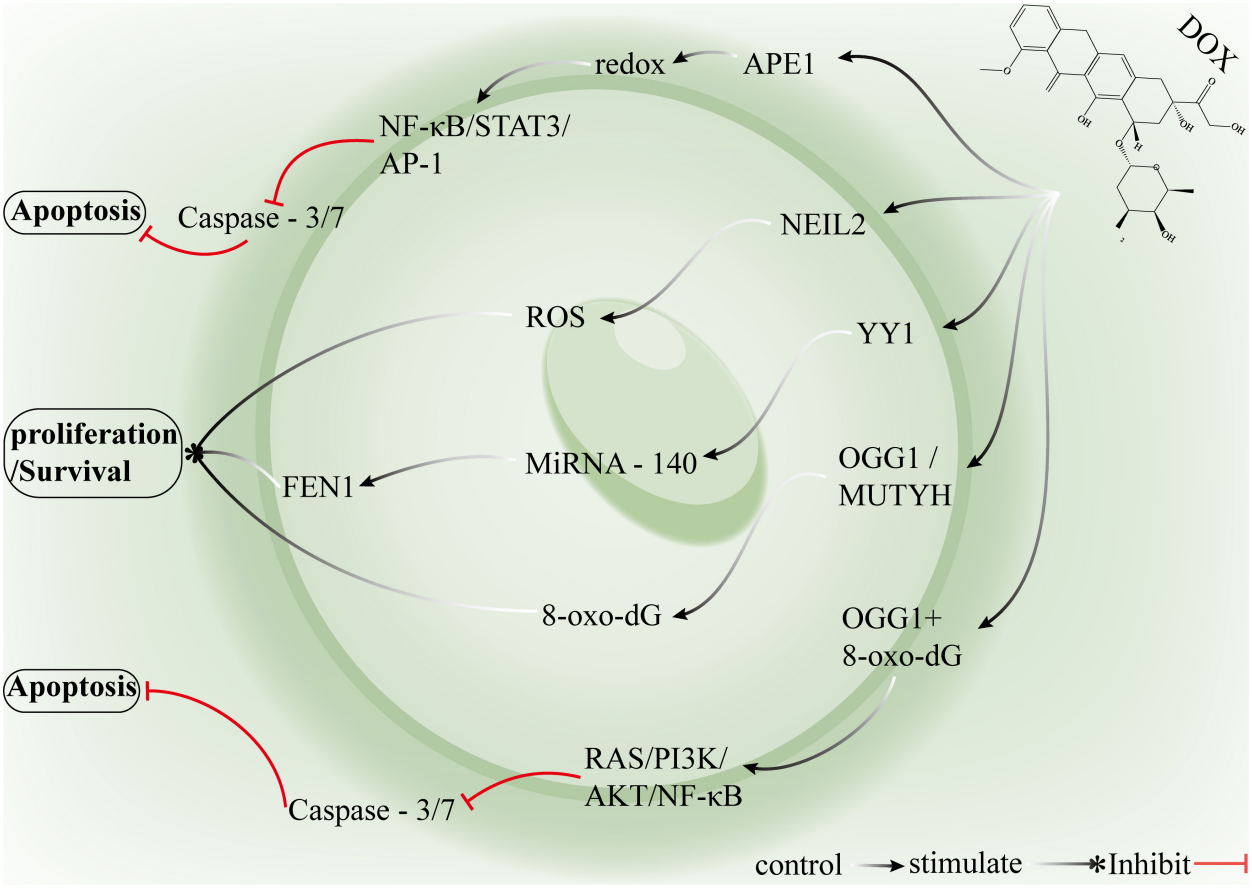


**Fig. 4. Mechanisms by which key genes in the BER pathway and associated signalling networks mediate DOX resistance in breast cancer.** The redox activity of APE1 enhances the DNA-binding capacity of NF-$\kappa$B, STAT3, and AP-1, which promotes the expression of survival genes and indirectly suppresses caspase-3/7–mediated apoptosis. Through the modulation of oxidative stress responses and the transcription of antioxidant genes, Ref-1 enables cancer cells to withstand the high ROS burden induced by DOX. OGG1 and MUTYH rapidly recognize and excise 8-oxo-dG and its mismatched bases, markedly reducing the extent of DOX-induced DNA damage. The OGG1–8-oxoG complex can directly activate RAS, driving downstream PI3K/AKT and NF-$\kappa$B pathways to inhibit apoptosis and increase cellular survival. The upregulation of NEIL2 further facilitates the repair of oxidative DNA lesions. YY1 activates miR-140, leading to FEN1 overexpression, which accelerates the BER process and ultimately results in a pronounced drug resistance phenotype in breast cancer cells. Apurinic/apyrimidinic endonuclease 1 (APE1): A bifunctional protein with redox activity that regulates transcription factor activity and participates in DNA repair. YY1 transcription factor (YY1): A multifunctional transcription factor gene. 8-oxoguanine DNA glycosylase (OGG1): A DNA glycosylase in the BER pathway that recognizes 8-oxo-dG. MutY DNA glycosylase (MUTYH): A BER DNA glycosylase that prevents 8-oxo-dG–induced G:C→ T:A transversion mutations. 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG): A hallmark of oxidative DNA damage. Signal transducer and activator of transcription 3 (STAT3): A signal transducer and activator of transcription. Activator protein 1 (AP-1): A transcription factor complex responsive to oxidative stress and growth signals that regulates cell proliferation and survival. BER, base excision repair; ROS, reactive oxygen species; NEIL2, nei like DNA glycosylase 2; FEN1, flap structure-specific endonuclease 1; RAS, Rat sarcoma.

ondary damage cascades. Suppression of YY1 diminishes its inhibitory effect on miR-140, leading to FEN1 upregulation, whereas DOX-induced inhibition of p300-mediated acetylation increases NEIL2 expression, which further promotes resistance. Inhibition of the redox function of APE1 may restore caspase-3/7 activity and increase the effective intracellular concentration of DOX, resensitizing cells to the drug. The inhibition of FEN1 expression or the modulation of miR-140 expression may reduce BER efficiency and enhance drug cytotoxicity. The combination of BER-targeted inhibitors with DOX can selectively increase tumor sensitivity while minimizing the toxicity to single targets. Nanoparticle-based delivery systems or ADCs can specifically deliver these inhibitors to breast tumors or cancer stem cells. The measurement of APE1, FEN1, or NEIL2 expression or activity enables the identification of patients at high risk of resistance, which allows for personalized clinical treatment. Tumor heterogeneity results in variable target

expression, the protective role of BER in normal cells may induce systemic toxicity, and resistance mechanisms often exhibit redundancy [46,60]. Future strategies may require combined targeting of core BER enzymes alongside conventional chemotherapy to achieve higher selectivity and efficacy in DOX-based therapy.

### *3.4 NER–Mediated Mechanisms of DOX Resistance in Breast Cancer*

Compared with BER, NER is a more complex, multistep pathway that removes bulky, helix-distorting adducts and certain crosslinks. NER comprises two subpathways, transcription-coupled NER (TCR-NER; repairs lesions on actively transcribed strands) and global-genome NER (GGR-NER; surveys and repairs lesions across the entire genome) [61,62]. Excision repair cross-complementation 1 (ERCC1), a core NER excision factor, heterodimerizes with endonuclease XPF (3′-flap repair endonuclease Xpf) (ERCC4) to form an endonuclease complex that incises damaged oligonucleotide fragments. ERCC1 overexpression increases NER capacity in breast cancer cells and has been implicated in DOX resistance [63]. For example, Fu *et al*. [64] reported that the upregulation of ERCC1 promotes the acquisition of DOX resistance in breast cancer cells by accelerating the repair of drug-induced DNA lesions. Current *in vitro* models of DOX resistance, typically generated by stepwise dose escalation or selection with high drug concentrations, do not fully recapitulate clinical resistance because the durability of resistance and the proliferative capacity of cells during the posttreatment recovery phase are often not comprehensively evaluated [65–67]. Compared with control cells, breast cancer cells may achieve more efficient repair of DOX-induced lesions through the overexpression or activation of key NER genes (e.g., XPA, XPC, CSB/ERCC6, XPF/ERCC4, and ERCC1), which reduces DOX cytotoxicity and drives drug resistance [68]. For example, Busatto *et al*. [69] reported that the upregulation of NER factors (XPA, XPC, ERCC6/CSB, XPF) during DOX exposure enhances NER activity, enables the clearance of extensive DOX-induced damage, and attenuates drug toxicity. After drug withdrawal and prolonged culture, NER gene expression rebounds in parallel with proliferative recovery, culminating in a resistant phenotype.

BMP/OP-responsive gene (BORG) expression promotes the reactivation of proliferation-associated genes in dormant breast lesions, is strongly induced by DOX treatment, and enhances survival and resistance in TNBC cells [70,71]. For example, Gooding *et al*. [72] demonstrated that under DOX exposure or metabolic stress, BORG forms a complex with the ssDNA–binding protein replication protein A1 (RPA1). The BORG–RPA1 complex activates the NF-$\kappa$B signalling cascade, which increases NER, reduces DOX-induced DNA damage in TNBC cells, promotes cell survival, and increases resistance to DOX (Fig. 5).

ERCC1 forms a nuclease complex with XPF, and its overexpression significantly enhances NER efficiency, which reduces drug-induced cytotoxicity and promotes a resistant phenotype. XPA, XPC, CSB, and XPF are upregulated during both DOX treatment and the withdrawal phase, which enables breast cancer cells to rapidly repair NER lesions and maintain their proliferative capacity. BORG interacts with the ssDNA-binding protein RPA1 to activate the NF-$\kappa$B signalling pathway, which further increases NER activity and promotes resistance to DOX in TNBC. Although these core targets provide potential intervention opportunities, several limitations exist: conventional *in vitro* resistance models often use high-dose or gradually escalating drug regimens that do not fully recapitulate *in vivo* drug exposure and microenvironmental conditions, and key NER genes play essential roles in maintaining genomic stability in normal tissues such that direct inhibition may induce systemic toxicity. Future strategies may involve specific modulation of ERCC1, XPF, and other critical NER genes using small molecule inhibitors or RNA interference to attenuate repair capacity; strategies also include targeting BORG or its upstream regulatory pathways to reduce NF-$\kappa$B-mediated NER enhancement, which would enable personalized combination chemotherapy that improves DOX efficacy and preserves normal tissue safety.

### *3.5 MMR–Mediated Mechanisms of DOX Resistance in Breast Cancer*

MMR corrects replication-associated errors, including single-base mismatches and small insertion/deletion loops (IDLs), and is executed by two principal protein complexes: the MutS complex, which recognizes mismatches, and the MutL complex, which coordinates downstream repair events and the recruitment of accessory factors [73–75]. The perturbation of MMR function or MMR-dependent cellular responses to DOX, such as defective G2-phase cell cycle arrest, reduces tumor cell sensitivity to DOX [76,77]. In breast cancer, mutL homolog 1 (MLH1) and mutS homolog 2 (MSH2) can be inactivated by genomic deletion or epigenetic mechanisms (promoter hypermethylation), and the methylation status of the MLH1/MSH2 promoter has been proposed as a potential biomarker for DOX responsiveness [78]. Epigenetic silencing of MMR genes, most notably promoter hypermethylation of MSH2, can also drive DOX resistance [79]. For example, Logeswari Ponnusamy *et al*. [80] demonstrated by pyrosequencing that multiple CpG sites within the MSH2 promoter are hypermethylated in DOX-resistant MCF-7 and MDA-MB-231 sublines, which substantially reduce MSH2 mRNA and protein levels, disrupt MMR-dependent apoptotic signalling, and promote a resistant phenotype. Importantly, treatment with the DNA-demethylating agent 5-Aza-2′-deoxycytidine (5-Aza-2dC) or the histone deacetylase inhibitor trichostatin A (TSA) largely restores MSH2 expression, re-establishes MMR-dependent apoptosis, and significantly increases the sensitivity of resistant cells to DOX (Fig. 6).

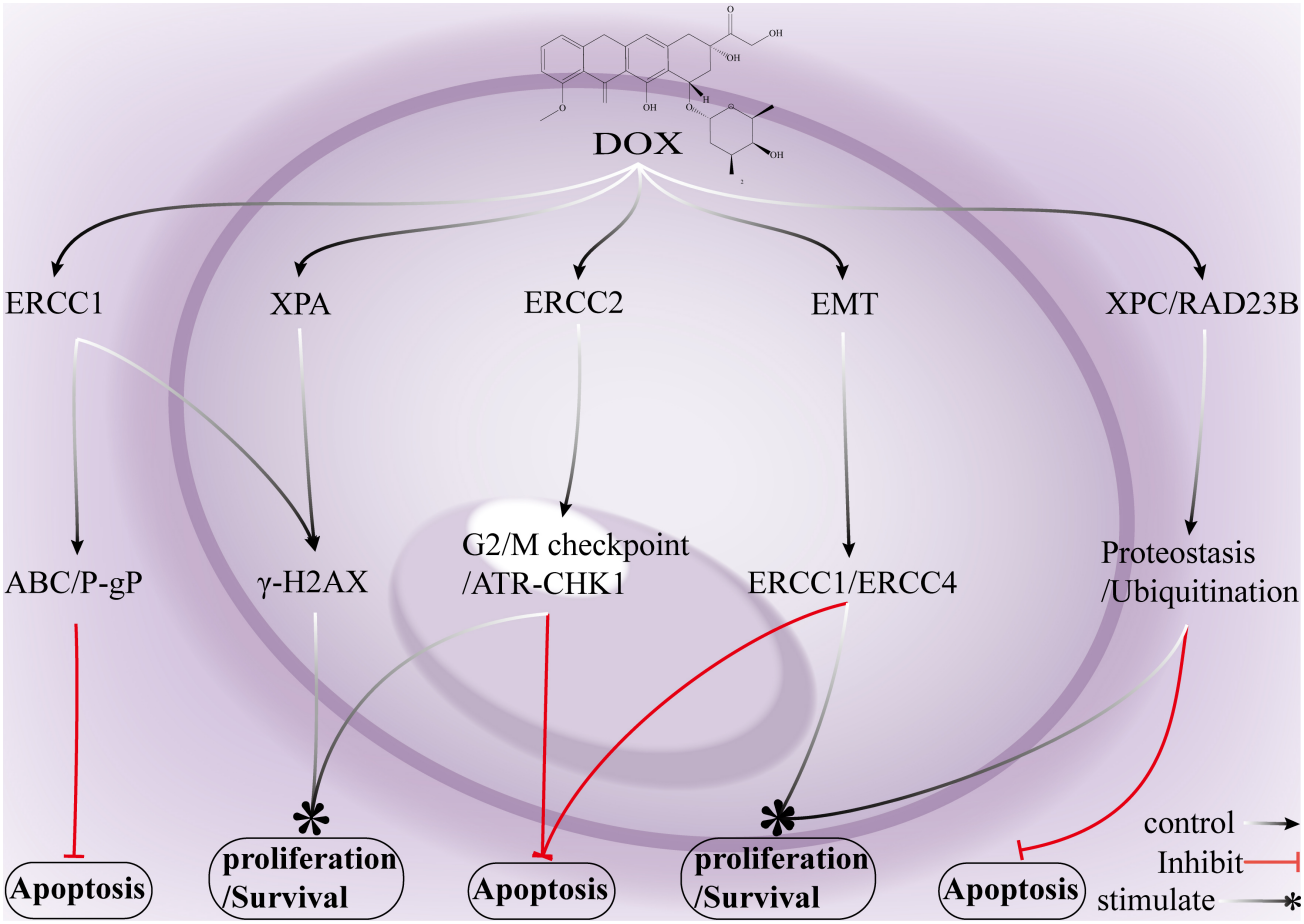


**Fig. 5. Mechanisms by which key genes in the NER pathway and associated signalling networks mediate DOX resistance in breast cancer.** ERCC1 upregulation cooperatively enhances drug efflux via P-gp/ABCB1, which reduces DOX-induced cytotoxicity and promotes the survival of breast cancer cells. Elevated ERCC1 typically facilitates the DDR, enabling tumor cells to withstand DOX treatment and acquire chemoresistance. Although DOX induces extensive DNA lesions in breast cancer cells, activation of the XPA-dependent NER machinery augments the repair capacity of these cells and increases the likelihood of cell survival. ERCC2 (XPD) strengthens the ATR–CHK1 signalling axis, maintaining tumor cells in a "pause-and-repair" state that further contributes to drug resistance. EMT enhances the expression of ERCC1/ERCC4 (XPF), which enables breast cancer cells to survive even under conditions of severe DNA damage. The XPC –RAD23B complex stabilizes NER protein homeostasis, which allows cells to "maintain equilibrium and continue survival" under DOX-induced stress. DNA damage recognition and repair factor (XPA): A core NER protein that recognizes bulky DNA lesions and recruits downstream repair factors. ERCC2 (XPD): A DNA helicase within the TFIIH complex that unwinds damaged DNA to initiate excision repair. XPC complex subunit (XPC): A DNA damage sensor that detects helix-distorting lesions and triggers global-genome NER. RAD23 nucleotide excision repair protein B (RAD23B): An accessory NER that forms a complex with XPC and stabilizes its lesion-recognition function. ERCC4 (XPF): A structure-specific endonuclease that cleaves the 5′ side of DNA lesions during NER. ATP-binding cassette transporters (ABC transporters): A family of membrane proteins that are responsible for mediating ATP-dependent substrate transport. P-gp (ABCB1): A pivotal ABC transporter that functions as a drug efflux pump to reduce the intracellular accumulation of chemotherapeutic agents. NER, nucleotide excision repair; ERCC1, ERCC excision repair 1, endonuclease non-catalytic subunit; ATR, ATR checkpoint kinase; CHK1, protein kinase Chk1; EMT, epithelial–mesenchymal transition.

In MCF-7 and MDA-MB-231 cells exposed to DOX, hypomethylation of the MLH1 and MSH2 promoter regions leads to upregulation of mRNA and protein expression, which is thought to contribute to DOX tolerance. Conversely, hypermethylation of the MSH2 promoter results in reduced expression, accompanied by impaired MMR-dependent cell death. Treatment with demethylating agents or histone deacetylase inhibitors can restore MSH2 expression and significantly reverse resistance. These findings suggest that the methylation status of the MLH1 and MSH2 promoters may serve as a biomarker and that these genes may be therapeutic targets. The downstream mechanisms through which MMR activation influences resistance include the regulation of cell cycle checkpoints, such as the

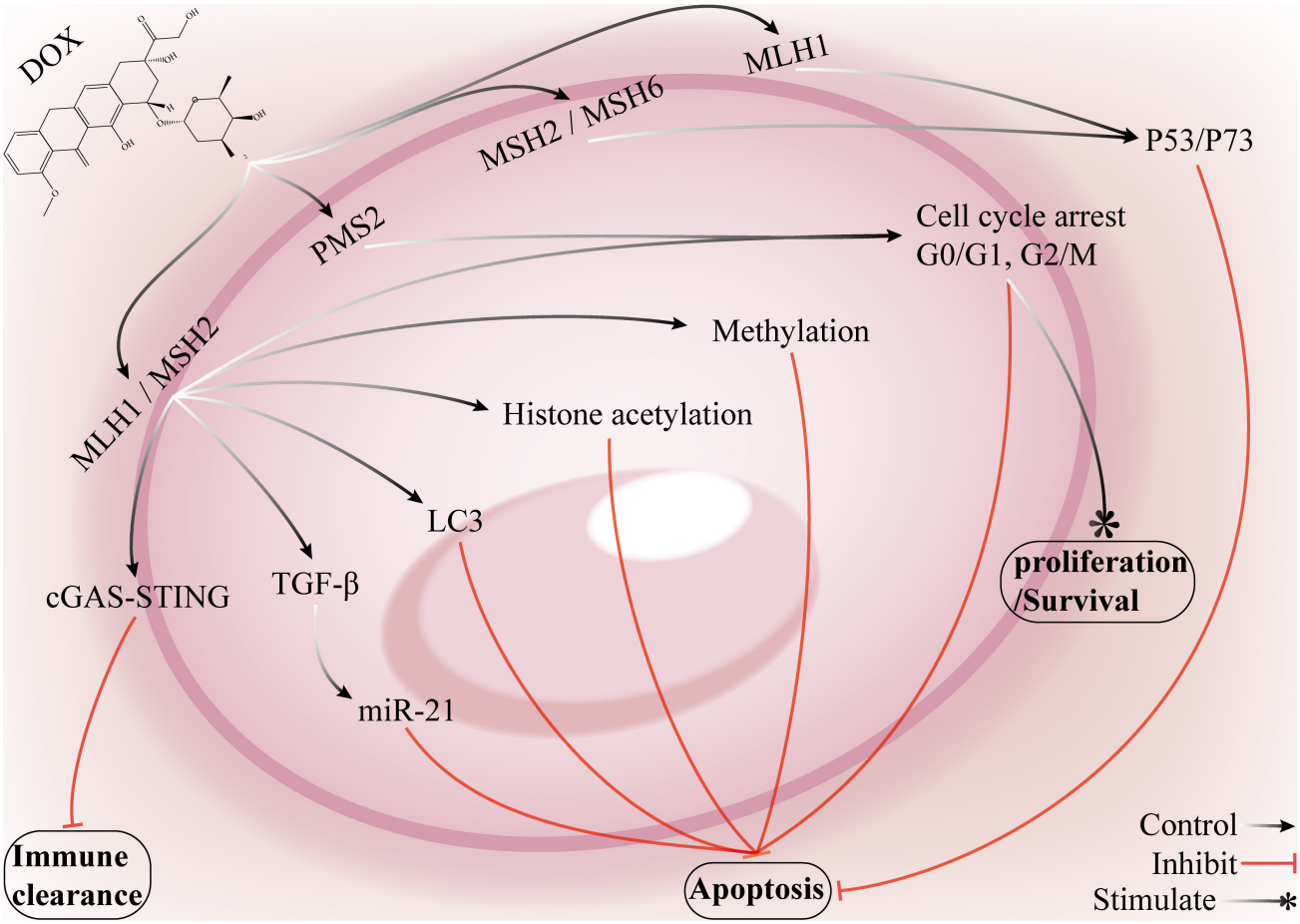


**Fig. 6. Mechanisms by which key genes in the MMR pathway and associated signalling networks mediate DOX resistance in breast cancer.** The promoter methylation of MSH2 and MLH1 can lead to reduced mRNA and protein expression, impairing the ability of the cell to sense DNA damage and attenuate apoptosis, which ultimately promotes DOX resistance in breast cancer cells. MSH2 activity is also modulated by epigenetic mechanisms such as histone acetylation, which affects its capacity for DNA damage recognition and repair and further reinforces the drug-resistant phenotype. Loss of MSH2 or MLH1 function suppresses the cGAS–STING signalling pathway, diminishing antitumor immune clearance; this loss may also activate TGF-$\beta$ signalling to upregulate miR-21, which potentially induces the expression of the autophagy-related protein LC3, weakens P53/P73-mediated apoptotic signalling, and contributes to cell cycle arrest. The convergence of these molecular events collectively enhances breast cancer cell survival and ultimately drives resistance to DOX. cGAS–STING: A cytosolic DNA-sensing pathway that detects aberrant DNA, activates type I interferon responses and contributes to antitumor immunity. Transforming growth factor-$\beta$ (TGF-$\beta$): A multifunctional cytokine involved in proliferation, differentiation, epithelial–mesenchymal transition, and immune regulation. miR-21: An oncogenic microRNA that suppresses tumor-suppressor genes and promotes proliferation, survival, and chemoresistance. Microtubule-associated protein 1 light chain 3 (LC3): A canonical autophagy marker essential for autophagosome formation and cellular degradation processes. P53/P73: Tumor suppressor genes that regulate apoptosis, DNA repair, and cell cycle control. MMR, mismatch repair; MSH2, mutS homolog 2; MLH1, mutL homolog 1.

G2/M checkpoint, and the induction of cell death. Reliance on a single biomarker to predict resistance remains challenging because of tumor heterogeneity, which may compromise therapeutic evaluation. Future strategies may involve combination therapies that target epigenetic regulation and the establishment of precise molecular diagnostic systems for the dynamic monitoring of MLH1/MSH2 methylation and expression levels. This approach could guide personalized therapy and improve both the clinical feasibility and the reversal of drug resistance.

## 4. Targeting the DDR for DOX Resistance in Breast Cancer

### *4.1 Drug Combination Targeted Therapy*

Combination therapies that pair DOX with inhibitors of DDR pathways can overcome resistance driven by enhanced repair capacity. Poly (ADP–ribose) polymerase (PARP) inhibitors block the repair of SSBs, allowing unrepaired SSBs to collapse into lethal DSBs. Inhibitors of ataxia telangiectasia and Rad3-related (ATR) or checkpoint kinases 1 and 2 (CHK1/CHK2) disrupt the replication-

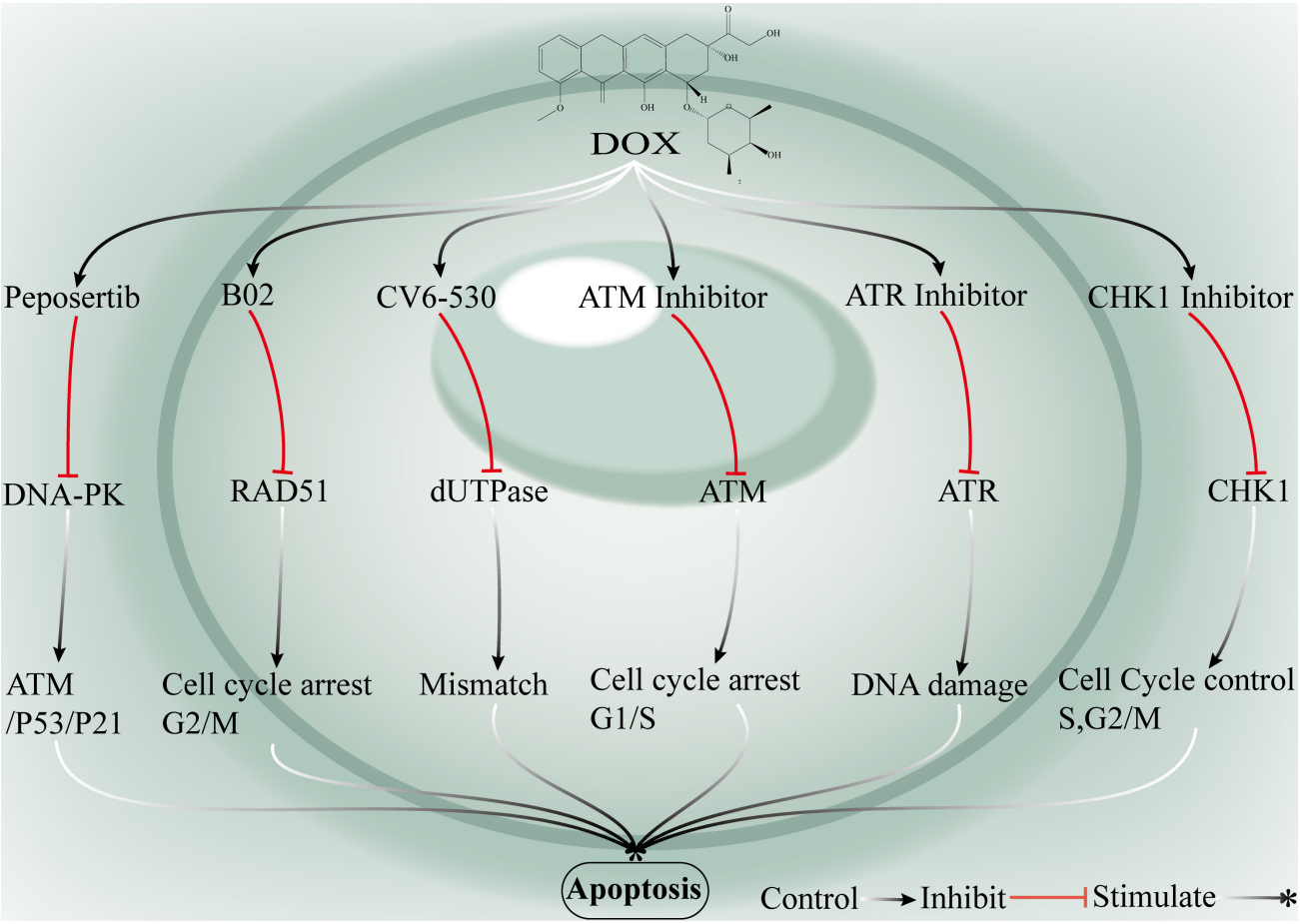


**Fig. 7. Synergistic strategies to overcome breast cancer chemoresistance via targeted inhibition of DDR pathways.** DNA-PK inhibitors suppress DNA-PK activity and consequently activate the ATM–P53–P21 signalling axis, which induces cell cycle arrest and apoptosis. B02, a RAD51 inhibitor, disrupts HR repair and perturbs G2/M phase regulation. CV6-530 inhibits deoxyuridine 5′-triphosphate nucleotidohydrolase (dUTPase) activity, which leads to the accumulation of uracil misincorporation and triggers the DDR. ATM inhibitors block ATM activity, causing cell cycle arrest at the G1/M checkpoint, suppress ATR signalling and impair the progression of DDR. CHK1 inhibitors inactivate CHK1, resulting in S-phase and G1/M arrest. When combined with DOX, these inhibitors synergistically enhance apoptotic responses in breast cancer cells, ultimately promoting tumor cell death. Ataxia-telangiectasia mutated (ATM): A master kinase that senses DSBs and activates the DDR, including the P53/P21 pathway. P21: A P53-inducible cyclin-dependent kinase inhibitor that blocks cell cycle progression into S phase or G2/M. ATM and Rad3-related (ATR): A key kinase that detects replication stress and initiates DNA damage checkpoint signalling. Checkpoint kinase 1 (CHK1): A checkpoint regulator essential for the initiation of the DDR and cell cycle arrest. CV6-530: A dUTPase inhibitor that induces uracil misincorporation and DNA base mispairing.

stress response and S/$G_2$ checkpoint, which promotes replication-fork collapse. Ataxia telangiectasia mutated (ATM) inhibitors combined with DNA-PKcs inhibitors cooperatively impair HR and NHEJ. WEE1 (a tyrosine kinase that restrains CDK activity) inhibitors and cyclin-dependent kinase 1/2 (CDK1/2) inhibitors abrogate the G2M checkpoint, forcing DNA-damaged tumor cells into mitosis and precipitating mitotic catastrophe and apoptosis [81,82]. Inhibitors of ATR, CHK1/2, and DNA-PK sensitize TNBC cells by disabling key repair mechanisms and increasing DOX cytotoxicity, which can help overcome drug resistance [83]. For example, Kevin J. Lee *et al.* [68] reported that ATM inhibition impairs the DSB-repair capacity of breast cancer cells, increasing their DOX sensitivity and apoptosis rates. ATR inhibitors block ATR kinase activity and the cellular response to single-strand lesions and stack replication forks, which leads to the accumulation of DNA damage and cell death. CHK1/CHK2 inhibitors attenuate checkpoint control during DNA damage and replication stress, which prevents timely repair and promotes apoptosis. DNA-PK inhibitors inhibit DNA-PK kinase activity and the cellular DSB response, which results in unrepaired lesions and subsequent cell death. Targeting HR directly enhances DOX efficacy: RAD51 inhibitors markedly increase DOX cytotoxicity by blocking HR-mediated repair and inducing cell cycle arrest, mitochondrial dysfunction,

and apoptotic signalling [84]. For example, Schürmann *et al*. [30] demonstrated that the RAD51 inhibitor B02 induces $G_2$/M arrest, causes mitochondrial damage, and activates apoptosis, which increases DOX-induced cytotoxicity in breast cancer cells.

Deoxyuridine 5′-triphosphate nucleotidohydrolase (dUTPase) inhibitors promote the incorporation of aberrant uracil into DNA and induce DNA damage. When DNA damage is induced by fluoropyrimidines or DOX, inhibition of dUTPase impairs the ability of the cell to prevent uracil incorporation and to process the resulting lesions, which results in the accumulation of lethal DNA damage and triggers apoptosis in breast cancer cells [85]. Compared with DOX monotherapy, the combination of DOX with a dUTPase inhibitor increases the number of DNA DSBs and suppresses their repair, which helps to overcome DOX resistance [86,87]. For example, Davison *et al*. [88] reported that DOX induces DSBs in breast cancer cells and that TNBC cells adapt to persistent DNA damage through metabolic reprogramming, which leads to the upregulation of new pyrimidine biosynthesis, a change that supports resistance. dUTPase inhibitors drive uracil incorporation, generate base mismatches, and cause the accumulation of fatal DNA lesions that ultimately induce apoptosis in TNBC cells (Fig. 7).

The combination of DOX with inhibitors of DDR pathways, such as PARP, ATR, CHK1/2, ATM, DNA-PKcs, RAD51, and dUTPase inhibitors, can increase DOX-induced DNA damage accumulation through multiple mechanisms, including blockade of single-strand break repair (SSBR), disruption of the replication stress response, inhibition of HR and NHEJ, and abrogation of the G2/M checkpoint. This leads to a significant increase in apoptosis in breast cancer cells. The rationale for such targeted combination strategies lies in their strong synergistic effects, which allow for enhanced antitumor activity at reduced doses of DOX while overcoming resistance associated with elevated DNA repair capacity [88–90]. Clinical translation remains challenging because of factors such as limited drug bioavailability, off-target effects, toxicity to normal cells, and the potential for tumor cells to develop new resistance via alternative repair pathways. Currently, this strategy is primarily at the preclinical stage, but some ATR inhibitors have entered phase I trials where the goal is to demonstrate tolerability and preliminary efficacy, although large-scale registration trials have not yet been conducted [91]. The combination of DOX with DDR inhibitors has substantial therapeutic potential in breast cancer, particularly TNBC, but further optimization of drug properties and combination regimens is needed to facilitate clinical application.

### *4.2 NcRNA–Mediated Sensitization Strategy*

NcRNAs are functional RNA species transcribed from the genome that are not translated into proteins. Major classes include lncRNAs, miRNAs, and circular RNAs (circRNAs) [92,93]. MiRNAs are short (~18–25 nt), single-stranded RNAs whose expression is initiated by RNA polymerase II-mediated transcription. miRNAs regulate gene expression in a posttranscriptional manner by base pairing with target sites (most commonly within 3′ untranslated regions, 3′UTRs) to repress translation or promote mRNA decay [94]. In p53-mutant breast cancer cells, dysregulation of miR-30c enables more effective activation of DDR mechanisms in response to DOX-induced lesions, which reduces DOX cytotoxicity. Conversely, miR-30c can act as a sensitizer of DDR proteins and increase DOX sensitivity in resistant cells [95]. For example, Shu Lin *et al*. [96,97] demonstrated that miR-30c directly targets the 3′ UTRs of FA complementation group F (FANCF) and the translesion-synthesis polymerase deoxycytidyl transferase (REV1), which suppresses their expression and increases breast cancer cell sensitivity to DOX. p53 mutation is associated with reduced miR-30c expression and the concomitant upregulation of FANCF and REV1 expression, which contributes to drug resistance. The expression of miR-21 has been reported to inversely correlate with the levels of DDR proteins under certain conditions: high miR-21 expression reduces DNA repair activity and increases DOX sensitivity. Circular RNA circ-21 (a covalently closed circRNA) modulates this axis by sponging miR-21; through the regulation of miR-21, circ-21 may alter PARP-1a expression and affect tumor cell sensitivity to DOX [98,99]. For example, Ana R. Rama *et al*. [100] reported that miR-21 overexpression in DOX-resistant cells decreases PARP-1 expression, impairs the DDR and influences cell survival. Conversely, circ-21 relieves the miR-21-mediated repression of PARP-1, which restores PARP-1 levels and enhances DDR capacity; this is associated with the suppression of proliferation, migration, and angiogenesis, increased apoptosis, and increased DOX sensitivity [85–87]. These reports underscore the context-dependent role of the miR-21/circ-21/PARP-1 axis in the modulation of DNA repair and cell fate and highlight ncRNA-based approaches as promising strategies to sensitize breast tumors to DOX.

lncRNAs regulate DOX resistance through complex molecular mechanisms, primarily by promotion of tumor cell proliferation, inhibition of apoptosis, upregulation of drug efflux transporters, modulation of DDR pathways (either activation or repression of repair genes), induction of autophagy, transfer of resistance factors through exosomes, and an increase in invasion and metastasis [101,102]. Some lncRNAs act as negative regulators of resistance and increase tumor cell sensitivity to DOX. The lncRNA H19 negatively regulates PARP1 expression, which is positively correlated with breast cancer cell sensitivity to DOX, and can function as a sensitizing target to increase DOX efficacy [90]. For example, Yu Wang *et al*. [103] reported that H19 downregulates PARP1 in DOX-treated breast cancer cells and that H19 knockdown increases PARP1 expression and

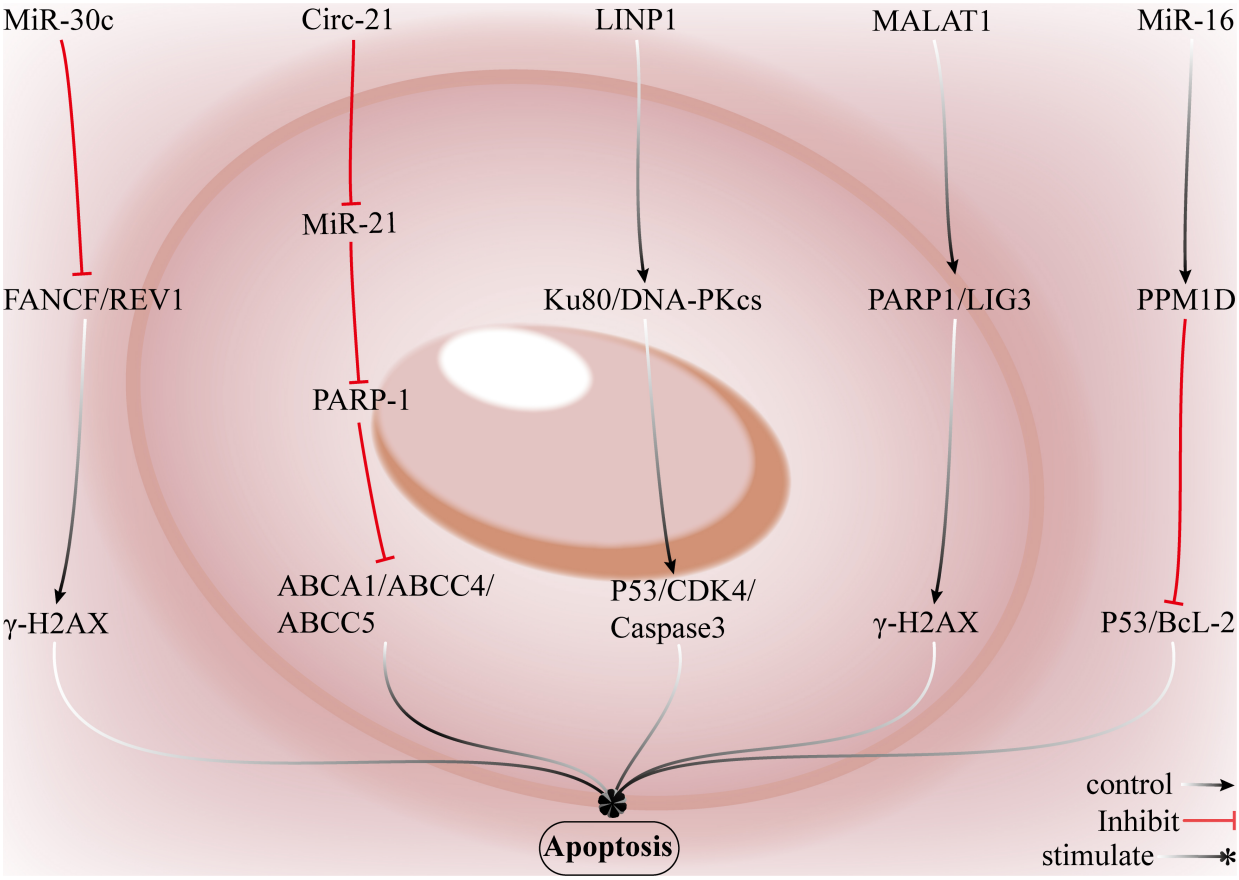


**Fig. 8. Strategies for reversing DOX resistance in breast cancer through ncRNAs.** LncRNAs, such as lncRNA in non-homologous end joining pathway 1 (LINP1), increase cellular resistance to DOX-induced DNA DSBs by upregulating key components of the NHEJ pathway, including Ku80 and DNA-PKcs, to promote cell survival. CircRNAs, such as circ-21, modulate miR-21 to suppress PARP-1 expression or activity and may synergistically regulate multidrug resistance–associated ATP-binding cassette transporters (ABCA1, ABCC4, and ABCC5), which drives tumor cell proliferation and survival. miR-30c impairs the DDR by targeting core factors of the Fanconi anaemia pathway and translesion synthesis machinery, namely, FA complementation group F (FANCF) and deoxycytidyl transferase (REV1), resulting in $\gamma$-H2AX accumulation and apoptosis. MiR-16 targets PPM1D, which attenuates phosphatase activity during DDR signalling and indirectly modulates DNA repair efficiency and susceptibility to apoptosis. MALAT1 promotes alternative nonhomologous end joining (alt-NHEJ) by interacting with PARP1 and LIG3, which leads to increased $\gamma$-H2AX accumulation and pathway activation, ultimately triggering apoptosis. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1): A LncRNA that regulates gene expression and stabilizes DDR complexes. Poly(ADP-ribose) polymerase 1 (PARP1): A key DNA damage sensor and enzymatic mediator of single-strand break repair (SSBR) and alt-NHEJ. DNA ligase III (LIG3): A ligase essential for alt-NHEJ and base excision repair. LINP1: LncRNA implicated in the regulation of the DDR. FANCF: A core component of the Fanconi anaemia pathway required for interstrand crosslink repair. REV1: A Y-family DNA polymerase involved in translesion DNA synthesis. Protein phosphatase, $Mg^{2+}/Mn^{2+}$ dependent 1D (PPM1D): A serine/threonine phosphatase that negatively regulates DDR signalling.

enhances cellular sensitivity to DOX, whereas H19 overexpression reduces PARP1 expression and restores resistance [103,104] (Fig. 8).

Restoration or overexpression of miR-30c suppresses FANCF and REV1 expression, which increases the sensitivity of breast cancer cells to DOX. Circ-21 enhances the antitumor efficacy of DOX by sequestering miR-21 and subsequently restoring PARP-1 expression. The lncRNA H19 negatively regulates PARP1, and silencing H19 upregulates PARP1 expression and sensitizes breast cancer cells to DOX. Most therapeutic miRNAs, lncRNAs, and circRNAs are prone to nuclease degradation, exhibit restricted tissue distribution, and display low cellular uptake *in vivo*. Achieving effective intratumoral concentrations often requires dose escalation, which in turn amplifies their inherent pleiotropic activities; this leads to gene expression perturbations in normal tissues and increases the risk of off-target effects. Although delivery technologies [105], such as lipid nanoparticles, polymeric nanocarriers, viral vectors, and chemically modified nucleic acids, can improve molecular stability and tumor uptake, they may also introduce new challenges, including nonspecific accumulation

in normal tissues, immune activation, and long-term alterations in gene-regulatory networks [106].

### *4.3 Targeted Intervention With NPs*

NPs are chemical entities isolated from plants, animals, microorganisms, or marine sources and are characterized by high structural complexity and diverse biological activities [107]. Compared with typical synthetic small molecules, NPs generally have higher molecular weights, a larger fraction of $sp^3$-hybridized carbons, more hydrogen-bond donors and acceptors, and lower predicted cLogP values [108]. As they act on multiple targets in a synergistic manner, NPs can disrupt the DDR equilibrium in drug-resistant breast cancer cells and can markedly potentiate DOX-mediated cytotoxicity [109,110]. Isorhamnetin (IS) is a naturally occurring flavonoid found in vegetables, fruits, and medicinal herbs. As a sensitizer of DOX-resistant breast cancer cells, IS enhances DOX cytotoxicity and inhibits tumor growth by increasing intracellular DOX accumulation (via downregulation of P-gp/ABCB1), impairing DDR pathways to reduce repair efficiency and modulating multiple signalling cascades that suppress cell proliferation [111,112]. For example, T. Yang *et al*. [113] demonstrated that in DOX-resistant breast cancer cells, IS induces ROS production and consequent DNA damage, leading to $G_2$/M cell cycle arrest. IS also downregulates BCL-2, promotes caspase-3 cleavage, and triggers apoptosis. In addition, IS activates AMPK in a ROS-dependent manner and inhibits the mTOR/p70S6K signalling axis. These coordinated effects synergize to sensitize resistant cells to DOX to effectively overcome DOX resistance.

Morin is a naturally occurring flavonoid found in elm and mulberry species (family Ulmaceae and *Morus* spp.) and in traditional medicinal herbs such as *Phellodendron* and *Glycyrrhiza* (liquorice) [114]. Morin markedly sensitizes DOX-resistant breast cancer cells; combined treatment with morin and DOX inhibits proliferation and promotes the apoptosis of resistant cells *in vitro*, and this cotreatment also significantly reduces tumor volume and weight in mouse xenograft models [115]. Moreover, morin disrupts both the accumulation and the repair of DNA damage in breast tumor cells, which impairs the ability of resistant cells to resolve drug-induced lesions, reverses resistance and enhances antitumor efficacy [116]. For example, Maharjan *et al*. [117] demonstrated that morin increases $\gamma$-H2AX levels but downregulates RAD51 and Ku80 expression, thus compromising the DDR and reducing breast cancer cell survival. In addition, morin increases the phosphorylation of AMP-activated protein kinase (AMPK) and LKB1 (p-AMPK, p-LKB1) and inhibits the phosphorylation of mTOR/p70S6K; morin also modulates MAPK signalling and reduces p-AKT and p-glycogen synthase kinase 3$\alpha/\beta$ (GSK3$\alpha/\beta$) levels. These convergent effects promote tumor cell death and potentiate the chemosensitizing activity of morin (Fig. 9).

IS enhances the cytotoxicity of DOX by inhibiting P-gp/ABCB1, increasing intracellular DOX accumulation, inducing the generation of ROS, and triggering substantial DNA damage. This is accompanied by G2/M cell cycle arrest, downregulation of BCL-2, and activation of caspase-3. IS further sensitizes resistant cells through ROS-mediated activation of AMPK, which suppresses mTOR/p70S6K signalling. Morin promotes apoptosis and inhibits cell proliferation through the upregulation of $\gamma$H2AX expression, downregulation of RAD51 and Ku80 expression, and modulation of AMPK/mTOR, MAPK, and AKT/GSK3 signalling. Due to their multitarget synergistic effects, natural flavonoids generally exhibit potent sensitizing activity with relatively low toxicity, and IS may even confer cardioprotective effects against DOX-induced toxicity. Clinical translation is currently limited by low bioavailability, suboptimal pharmacokinetics, potential off-target effects, and unclear dose–response relationships [118]. Systematic studies that have assessed whether long-term drug administration induces new mechanisms of tumor resistance are lacking [113,119]. IS and morin possess a clear biological rationale and promising clinical development potential for reversing DOX resistance, but their effective clinical translation will require further *in vivo* efficacy validation, comprehensive toxicological evaluation, and early-phase clinical trials.

## 5. Conclusions and Future Perspectives

The poor clinical efficacy of DOX in the treatment of breast cancer is largely attributable to DDR-mediated resistance.

Different DDR pathways do not operate in isolation, but rather, they show competitive, cooperative, and compensatory interactions. These interactions depend on the cell cycle phase, end-processing status, and availability of key repair factors [120]. When HR is impaired or inhibited, tumor cells often compensate by upregulating classical NHEJ and the more error-prone alternative end-joining (alt-EJ/TMEJ), which is mediated mainly by DNA polymerase theta (POLQ). These pathways then “hijack” DSB repair and sustain survival at the cost of increased genomic instability [121]. This plasticity among pathways explains why single-target therapies often result in rapid resistance. This includes reversion mutations in HR genes, such as BRCA, restoration of HR activity, or increased use of the alt-EJ pathway as an escape mechanism. In HR-deficient contexts, combined strategies based on “synthetic lethality plus blockade of backup pathways” can help. For example, pairing PARP inhibitors with POLQ or DNA-PK inhibitors can prevent pathway switching and increase therapeutic lethality [122]. However, simultaneous inhibition of multiple DDR pathways markedly increases toxicity in normal rapidly dividing tissues. Successful clinical translation, requires precise patient stratification, careful optimization of dosing and scheduling, and dynamic monitoring through

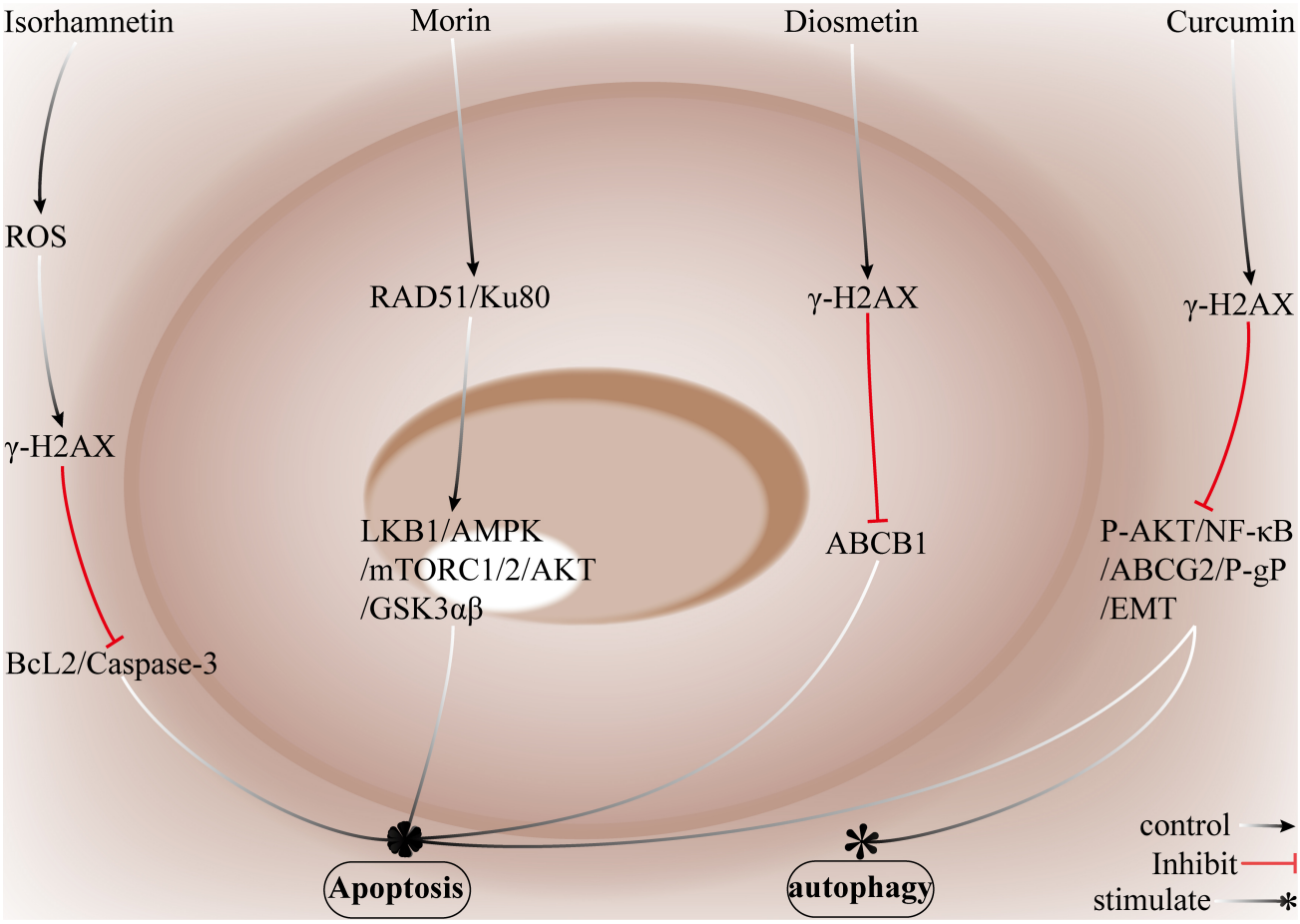


**Fig. 9. Strategies by which natural compounds restore DOX sensitivity in breast cancer.** IS increases the generation of ROS, induces DNA damage characterized by $\gamma$-H2AX accumulation, suppresses the antiapoptotic protein BCL-2, and activates Caspase-3, which directly promotes apoptosis. Morin primarily acts through the regulation of metabolic and DNA repair pathways, as this compound activates the LKB1/AMPK axis and inhibits the downstream mTORC/AkT/GSK3$\alpha\beta$ survival cascade, which suppresses the expression of DNA repair proteins such as RAD51 and Ku80; this in turn increases DOX-induced DNA damage and apoptotic signalling. In overcoming multidrug resistance, diosmetin attenuates drug efflux by directly inhibiting P-gp/ABCB1 activity, which leads to intracellular DOX accumulation and indirectly promotes apoptosis. Curcumin exerts multiple effects: it not only inhibits prosurvival and metastatic signalling pathways, including p-AkT/NF-$\kappa$B/EMT, but also downregulates multiple efflux transporters, such as ABCB1 and ABCG2, which comprehensively dismantles cellular resistance mechanisms. BCL2: An antiapoptotic protein that inhibits mitochondrial outer membrane permeabilization and suppresses caspase activation. LKB1 (Liver Kinase B1/STK11): A tumor-suppressor kinase that regulates cell polarity, metabolism, and AMPK signalling. AMP-activated protein kinase (AMPK): A central energy-sensing kinase that maintains metabolic homeostasis and regulates cellular responses to stress. Mechanistic target of rapamycin complexes 1 and 2 (mTORC1/2): Two distinct mTOR-containing complexes that control cell growth, metabolism, and survival. Glycogen synthase kinase 3$\alpha/\beta$ (GSK3$\alpha/\beta$): Serine/threonine kinases involved in metabolism, cell cycle regulation, and signalling pathways such as the Wnt and PI3K–AKT pathways. Phosphorylated AKT (p-AKT): The activated form of AKT that promotes cell survival, proliferation, and metabolic adaptation. ABCG2 (ATP-binding cassette subfamily G member 2; also known as BCRP): A drug efflux transporter associated with multidrug resistance. Epithelial–mesenchymal transition (EMT): A cellular program in which epithelial cells acquire mesenchymal characteristics that enhance motility, stemness, and therapeutic resistance.

**Table 1. Mechanisms, advantages, and limitations of intervention strategies for DOX-resistant breast cancer.**

| Strategies | Drugs | Advantages | Disadvantages | Applicable scenarios | Challenges |
|---|---|---|---|---|---|
| Small molecule inhibitor | PARP inhibitors, ATR inhibitors, CHK1 inhibitors, ATM inhibitors, WEE1 G2 checkpoint kinase (WEE1) inhibitors, CDK1/2 inhibitors, RAD51 inhibitors, dUTPase inhibitors. DNA-PKcs inhibitors | (1) Direct targeting of ATM, ATR, CHK1, CHK2, DNA-PK, or RAD51 can induce synthetic lethality or suppress compensatory escape pathways.<br>(2) These agents exhibit well-defined pharmacological activity, allowing for controlled dose modulation, and are suitable for combination therapy with DOX in clinical settings. | (1) Inhibition of multiple DDR pathways may lead to toxicity in normal, rapidly proliferating tissues, such as the bone marrow and intestinal epithelium.<br>(2) Single-target interventions are prone to the emergence of DOX resistance. Substantial patient heterogeneity underscores the need for precise molecular stratification to guide therapeutic selection. | (1) The applicability of these strategies in HR–deficient tumors relies on the compensatory upregulation of NHEJ or POLQ-mediated microhomology-mediated end joining (MMEJ).<br>(2) In patients with recurrent or DOX-resistant breast cancer, long-term and dynamic monitoring of pathway rewiring is required to guide treatment. | (1) Clinical toxicity is difficult to manage, with narrow therapeutic windows and a lack of highly selective small-molecule inhibitors—particularly for targets such as DNA polymerase theta (POLQ).<br>(2) Inadequate patient stratification further complicates clinical trial design, especially when combination strategies, safety assessment, and resistance monitoring must all be simultaneously addressed. |
| ncRNA | miR-30c, circ-21, LINP1, metastasis associated lung adenocarcinoma transcript 1 (MALAT1), MiR-16 | (1) These molecules may regulate DDR pathways and exhibit flexible mechanisms of action.<br>(2) They can also serve as biomarkers, as miRNAs are relatively stable in body fluids and may be used to predict DOX resistance in breast cancer. | (1) Delivery remains challenging, including issues of stability, target specificity, and achieving effective intratumoral concentrations.<br>(2) Nonspecific effects are a concern, as a single miRNA may target multiple genes, leading to off-target consequences. | (1) The context-dependent functionality of ncRNAs, the intricate nature of their regulatory networks, limited efficiency of *in vivo* delivery, and the risk of non-specific effects remain major obstacles to the successful clinical translation of ncRNA-targeted therapeutic strategies in breast cancer.<br>(2) Immune responses and *in vivo* toxicity are not yet fully understood, contributing to the slow pace of clinical translation. | (1) Delivery platforms require further optimization, and comprehensive studies on clinical dosing, safety, and off-target effects, as well as validation of biomarkers are needed.<br>(2) Regulatory and manufacturing challenges also remain significant for the development of ncRNA therapeutics. |

**Table 1. Continued.**

| Strategies | Drugs | Advantages | Disadvantages | Applicable scenarios | Challenges |
|---|---|---|---|---|---|
| Natural bioactive compounds (NPs) | Isorhamnetin (IS), Morin, Diosmetin, Curcumin | (1) These compounds generally exhibit low toxicity and good biocompatibility.<br>(2) They can serve as sensitizers in combination with DOX, enhancing the susceptibility of resistant breast tumors to DOX while mitigating adverse effects.<br>(3) Their multitarget activity not only modulates DDR but also affects transport proteins and key signalling pathways. | (1) Poor bioavailability and limited stability, such as low oral absorption and inefficient *in vivo* delivery, pose significant challenges.<br>(2) Their complex pharmacological mechanisms may lack sufficient specificity, and combination with DOX could carry potential risks.<br>(3) Clinical evidence remains limited, as most studies are still confined to *in vitro* or animal models. | (1) These strategies are applicable to DOX-resistant breast tumors, particularly when transport proteins and ABC pumps are upregulated.<br>(2) Long-term combination therapy may be required to delay the onset of resistance, with the potential to reduce DOX-associated toxicities, such as cardiotoxicity. | (1) Enhancing bioavailability remains a key goal, while comprehensive studies on systemic toxicity and pharmacokinetics are still needed.<br>(2) Clinical translation is challenging, particularly regarding dosing, combination regimens, and formulation strategies; clinical trial data remain relatively scarce. |

Note: This table summarizes the key points described in the text. The relevant references are cited in the corresponding section.

longitudinal tumor sequencing or circulating tumor DNA to detect early signs of resistance or pathway rewiring [123] (Table 1).

Careful selection and scheduling of DDR inhibitors are essential for maximizing antitumor benefits while minimizing detrimental effects on normal tissue repair. Promising complementary strategies to overcome DOX resistance include early detection and longitudinal monitoring of chemoresistance, optimization of drug formulation and dosing to increase intratumoral exposure, rational combinations of natural products with targeted small-molecule inhibitors and direct targeting of breast cancer stem cells. Natural phytochemicals, such as curcumin, piperine, and quercetin, have been reported to synergize with DOX to increase antitumor efficacy and delay the onset of resistance; moreover, these compounds also generally exhibit low toxicity and favourable biocompatibility. Ligand-coated polymeric nanoparticles, magnetic nanoparticles, liposomes, micelles, nanocages, and nanorods can enable more precise tumor targeting and improved DOX uptake. Targeting resistance-associated transporters and signalling networks, notably through ncRNAs, offers an additional route to suppress DDR activity, limit the development of resistance, and promote tumor cell apoptosis.

This review systematically summarizes the roles of MMR, BER, NER, HR, and NHEJ as central determinants of DOX resistance and evaluates the translational potential of DDR-targeted agents, ncRNA-based approaches, and NPs in reversing resistance. Future advances in multi-omics technologies and biomarker discovery should enable DDR defect-driven molecular subtyping of breast cancer and the design of personalized regimens to inform clinical decision-making. The reclassification of tumors according to DNA repair status is likely to yield novel insights for next-generation targeted therapies and more informative clinical trial designs. Elucidating DDR-mediated DOX resistance will provide both the theoretical foundation and practical guidance needed to accelerate the development of precision interventions for the treatment of DOX-resistant breast cancer.

## Author Contributions

YJW, XQL and WJW conducted the literature search and wrote the original draft. SBL and XHL designed the research and integrated and refined the key points. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflicts of Interest

The authors declare no conflicts of interest.

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