The molecular mechanisms of chemotherapeutic resistance in tumors (Review)

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Abstract. Chemotherapy remains a prevalent treatment for a wide range of tumors; however, the majority of patients undergoing conventional chemotherapy experience varying levels of chemoresistance, ultimately leading to suboptimal outcomes. The present article provided an in-depth review of chemotherapy resistance in tumors, emphasizing the underlying factors contributing to this resistance in tumor cells. It also explored recent advancements in the identification of key molecules and molecular mechanisms within the primary chemoresistant pathways.

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1. Introduction

The incidence of tumors is rising due to population growth, aging and advancements in tumor diagnostics (1), making malignant tumors a significant threat to human health and life (2,3). Cancer treatment options include surgery, radiotherapy, chemotherapy, targeted therapy, hormone therapy and immunotherapy (1), with chemotherapy being the most widely used across various cancer types. However, chemoresistance remains a complex clinical challenge, leading to the majority of cancer-related deaths (4,5). Understanding the mechanisms of chemoresistance is therefore essential for enhancing therapeutic efficacy, and the present article reviewed the latest developments in tumor chemoresistance. Notably, since numerous studies have already detailed the drug resistance mechanisms of molecular targeted therapies, the present review did not delve into those aspects (6-8).

Anatomical barriers that limit or obstruct the entry of foreign substances into target tissues or cells play a significant role in tumor chemoresistance. For example, in mammals, the blood-brain barrier, composed of tightly connected endothelial cells, basement membranes and astrocytes, restricts the passage of most chemotherapeutic drugs, thereby reducing their efficacy against central nervous system cancers. Mechanosensitive $Sox2^+$ tumor cells, for instance, develop chemoresistance by constructing a blood-tumor barrier around capillaries (9). Similarly, the blood-testis barrier, formed by testicular supporting cells, protects germ cells from toxic substances. Sertoli cells, which are resistant to apoptosis despite strong inflammatory stimuli (for example, LPS and IL-18), play a pivotal role in maintaining the homeostasis of the testicular environment, and this anti-apoptotic and anti-inflammatory capability further enhances their resistance to chemotherapy (10).

Chemotherapy resistance in cancer can be categorized into inherent and secondary resistance based on its origin. Inherent resistance refers to the presence of drug-resistant cells within the tumor tissue before treatment begins (11). This concept

suggests that drug resistance is a 'fait accompli', with relapse occurring once preexisting resistant cells repopulate (12). By contrast, secondary drug resistance arises when tumor cells develop resistance to chemotherapeutic drugs due to intracellular changes induced by the drugs themselves (Fig. 1).

Chemotherapy resistance can also be classified into primary drug resistance and multidrug resistance, depending on the response of tumor cells to chemotherapy agents (13). Primary drug resistance occurs when tumor cells develop resistance to a therapeutic drug after treatment, commonly due to decreased drug uptake or increased drug efflux. Multidrug resistance, on the other hand, involves tumor cells becoming resistant not only to the therapeutic agent but also to other chemotherapeutic drugs to which they have not been previously exposed. This phenomenon is driven by mechanisms such as enhanced drug efflux, increased DNA repair, neutralization of chemotherapeutic agents, closure of nuclear pores and tumor cell dormancy.

2. Mechanisms of action of chemotherapy drugs

Chemotherapeutic agents encompass a wide range of categories, including alkylating agents, antimetabolites, antibiotics and antitumor phytopharmaceuticals, among others. Although these agents employ diverse mechanisms of action, the majority must penetrate the cell nucleus to exert their therapeutic effects (Fig. 2).

Alkylating agents, such as cyclophosphamide and cisplatin, are capable of targeting both proliferative and non-proliferative cells. These agents possess active alkylating groups that generate electrophilic groups with positive carbon ions. These ions form covalent bonds with various nucleophilic groups within cells, leading to cross-linking between DNA molecules or between DNA and proteins, ultimately causing disruptions in DNA replication and transcription, culminating in cell death (14,15). Furthermore, alkylating agents have been shown to induce protein oxidation and acetylation, which can impair the lipid homeostasis of the nuclear membrane and destabilize the cellular genome (15). Cisplatin, a cis-alkylating agent, specifically induces cross-links within DNA double strands, resulting in the cessation of DNA replication and transcription, or even causing DNA strand breaks and apoptosis (16). As the first metal-based chemotherapeutic drug, cisplatin has been extensively used, though its side effects, including ototoxicity and nephrotoxicity, have posed significant challenges in its clinical application (17,18).

Antimetabolites, structurally similar to natural metabolites but lacking their corresponding biological functions, competitively inhibit and disrupt nucleic acid and protein synthesis, ultimately leading to cell death (19). The most notable example is 5-fluorouracil, which inhibits thymidine synthetase, thereby impairing DNA synthesis within the body (20).

Antitumor antibiotics, derived from microorganisms, exert their effects by directly damaging DNA or intercalating within it, thereby disrupting transcription (21). A key example is doxorubicin, which is extensively employed in the treatment of hematological malignancies, breast cancer and lung cancer (22).

Plant-derived antitumor agents, such as paclitaxel and vincristine, inhibit tumor cell proliferation by targeting microtubule proteins. Paclitaxel primarily prevents the depolymerization of microtubules during mitosis, whereas vincristine inhibits microtubule polymerization (23). Despite the clinical success of these plant-derived anticancer drugs, tumor resistance to them remains prevalent, particularly in some gastrointestinal cancers that exhibit resistance from the onset of chemotherapy.

3. Molecular mechanisms of chemotherapy resistance

Decreased drug entry into cells. Plant-derived chemotherapeutic agents, such as paclitaxel and vincristine, possess favorable lipid solubility, enabling them to permeate cells via passive diffusion through the lipid bilayer of the cell membrane (24,25). By contrast, cisplatin, a metal-based anticancer drug, increases its water solubility by replacing chloride ions with $Pt(NH_3)_2(H_2O)_2$. However, this substitution process occurs slowly, necessitating that cisplatin primarily enters cells through active transport mechanisms (26).

Research has identified that defective expression of copper ion transporter protein 1 (CTR1) correlates with reduced platinum accumulation in tissues, leading to decreased therapeutic efficacy of platinum-based drugs in various tumors (27). Under basal conditions, CTR1 is predominantly localized in the perinuclear region of cultured cells, but in the presence of copper complexes, CTR1 is highly expressed on the cell membrane, facilitating cisplatin's active transport. The uptake of cisplatin mediated by CTR1 depends on its metal-bound extracellular region, which is connected to the N-glycan chain at Asn15 and the O-glycan chain at Thr27 (28). Although cisplatin does not alter the subcellular localization of CTR1, co-localization studies using fluorescent cisplatin derivatives revealed their presence in CTR1-associated vesicular structures, indicating that cisplatin is endocytosed concurrently with CTR1 and transported into the cell (29).

Organic cation transporters (OCTs) are essential for the cellular uptake of endogenous cationic substrates, hydrophilic exogenous compounds, and platinum-based anticancer drugs. OCTs are highly expressed in the renal basement membranes of humans and mice, playing a significant role in mediating cisplatin uptake (30). Elevated levels of OCT2 in pre-chemotherapy biopsy samples have been associated with improved prognosis when treated with cisplatin-inclusive regimens (31). Conversely, in OCT2 knockout (-/-) mouse models, both nephrotoxicity and ototoxicity were significantly reduced following cisplatin treatment (32). Although overexpressing transport proteins exogenously is not yet feasible in clinical practice, current strategies focus on developing novel carriers, such as nanomaterial conjugates, to enhance the intracellular delivery of chemotherapeutic drugs. This approach aims to increase the intracellular concentration of these drugs, thereby enhancing their efficacy in tumor cell eradication.

Increased chemotherapy drug excretion. Members of the ABC protein transporter family, primarily located in cell membranes, are responsible for expelling cytotoxic substances, including chemotherapeutic drugs, out of the cell by utilizing ATP hydrolysis for energy (33). This process impedes the accumulation of therapeutic drug concentrations in target cells or organs, thereby contributing to chemoresistance (34). Moreover, ABC transporter proteins have been implicated

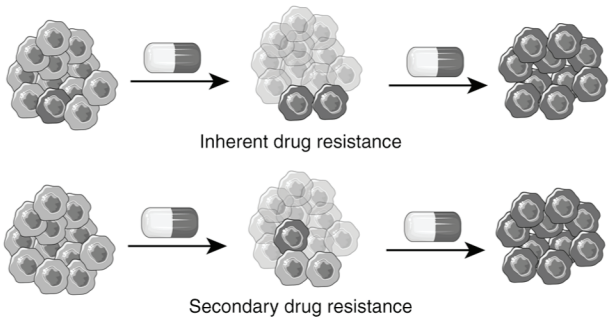

Figure 1. Inherent and secondary drug resistance: Drug resistance in tumor cells can be categorized into inherent and secondary types based on its origin. Inherent drug resistance arises from the pre-existence of drug-resistant cells within the tumor due to its heterogeneity. During chemotherapy, these resistant cells survive and become the dominant population, leading to overall tumor resistance. Secondary drug resistance, on the other hand, develops during chemotherapy as a result of the tumor cells' high genomic instability, enabling them to acquire resistance and subsequently survive treatment.

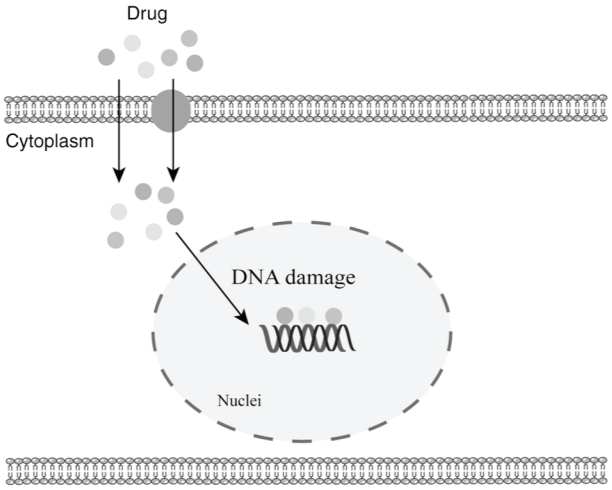

Figure 2. Chemotherapeutic drugs entering the nucleus to exert antitumor effects: While various chemotherapeutic agents employ different mechanisms of action, the majority must penetrate the cell nucleus to exert their antitumor effects.

in promoting tumor cell migration and invasion (35). The ABC transporter family is categorized into seven subgroups (ABCA-ABCG) comprising 48 proteins, based on sequence homology (36). All subfamilies, except the ABCF family, have been linked to tumor chemoresistance, with key members including ABCB1, ABCC1 and ABCG2.

The ABCB1 protein, also known as P-glycoprotein (P-gp), serves a physiological role in safeguarding sensitive tissues and the fetus from endogenous and exogenous toxins. It primarily facilitates the transport of lipid-soluble drugs, such as paclitaxel, vincristine and adriamycin (34,36-38). Although P-gp binding substrates like everolimus have shown potential in reversing chemoresistance *in vitro* and in animal models by interacting with extracellular binding epitopes, clinical trials have not yielded significant results, leaving the underlying mechanisms unclear. Developing inhibitors that induce conformational changes in ATP transport proteins remains a promising avenue for future research (34,39-41).

The ABCC1 protein, also known as multidrug resistance-associated protein 1 (MRP1), was the second drug resistance transporter identified after P-gp. MRP1 transports a wide array of pathophysiological substrates, including folic acid, bilirubin, anthracyclines, glutathione (GSH) and glucuronide conjugates, though it is less effective at transporting paclitaxel-like drugs compared with other ABC transporters (36,41-43). Tumor cells overexpressing MRP1 exhibit lower intracellular GSH levels and higher GSH efflux, leading to its designation as a GSH transporter protein. After GSH binds to chemotherapeutic drugs to form a complex, MRP1-mediated co-extrusion reduces the intracellular concentration of these drugs, contributing to tumor cell drug resistance (41,44).

ABCG2, also known as breast cancer resistance protein, was first identified in breast cancer-resistant tumors and functions as a hemi-transport protein, requiring homo- or heterodimerization to act as an effective transporter (45). Cryo-electron microscopy has revealed that ABCG2 can bind and transport chemotherapeutic agents such as topotecan and mitoxantrone, as well as P-gp inhibitors such as tariquidar (46).

Currently, the primary strategy for modulating the ABC transporter protein family involves targeting overexpressed proteins, but clinical benefits have been limited. Future research may focus on developing drugs that induce conformational changes in ABC transporter proteins, potentially offering a new direction for overcoming chemoresistance.

GSH and drug binding. GSH, a tripeptide consisting of glutamate, cysteine and glycine, is a critical component of the cellular antioxidant system, essential for tumor cells in scavenging reactive oxygen species (ROS) and neutralizing chemotherapeutic agents (47). Predominantly existing in its reduced form within the cell, GSH reacts with oxidizing agents such as ROS, converting to GSH disulfide (GSSG). Excess GSSG can be expelled from the cell or reduced back to GSH via GSH reductase. The intracellular GSH concentration typically ranges from 2-10 mM, ~1,000-fold higher than in the extracellular environment (2-10 μM) (47).

GSH also plays a critical role in ROS scavenging as part of the cellular antioxidant system. Elevated GSH levels in tumor cells safeguard them from ROS-induced DNA damage and apoptosis by neutralizing ROS during tumor growth. Research indicates that reducing GSH levels in tumor cells can elevate ROS levels, thereby enhancing the cytotoxic effects of therapeutic agents on these cells (48,49) (Fig. 3).

Moreover, GSH is involved in the neutralization of cytotoxic substances under physiological conditions, with numerous chemotherapeutic drugs, such as cisplatin and adriamycin, acting as binding substrates for GSH (50). Catalyzed by GSH-S-transferase (GST), GSH directly binds to electrophilic xenobiotics in the cytoplasm, preventing these chemotherapeutic drugs from entering the nucleus and exerting their inhibitory effects. The resulting GSH-drug conjugates are then exported from the cell via MRP1, thereby reducing the intracellular concentration of these drugs and contributing to the development of chemoresistance in tumor cells (51). Experimental evidence suggests that decreasing intracellular GSH levels can reverse cisplatin resistance and enhance its therapeutic efficacy (52).

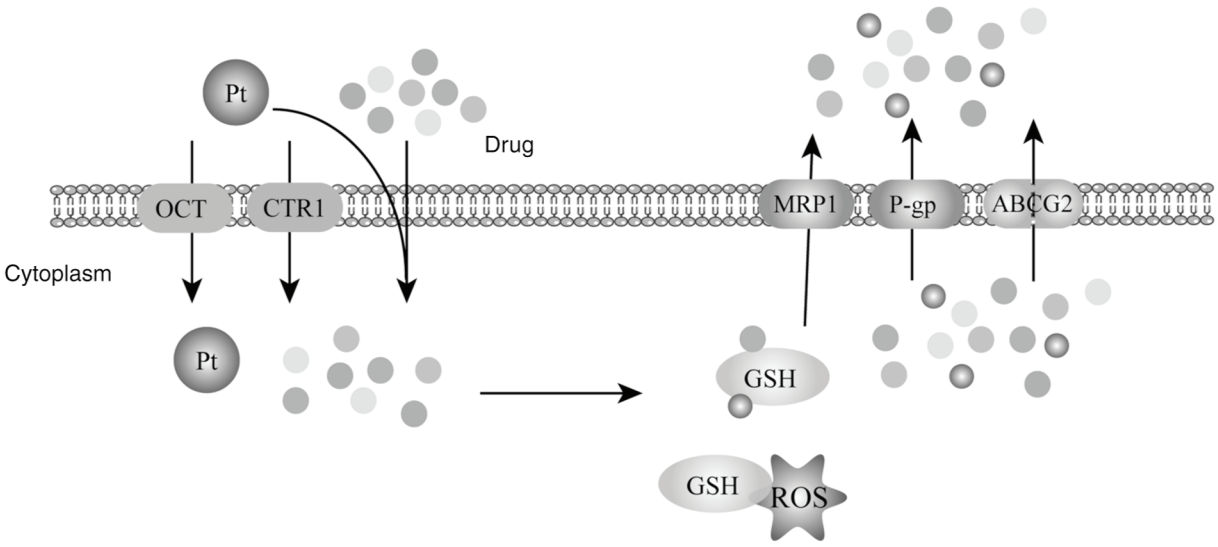

Figure 3. Mechanisms of drug resistance in the cell membrane and cytoplasm: Chemotherapeutic agents such as cisplatin enter cells through transporters such as CTR1 and OCT on the cell membrane. Within the cytoplasm, GSH functions as the primary redox buffer, neutralizing chemotherapeutic drugs and ROS to protect the nucleus from damage. Drugs that do enter the cytoplasm are often expelled from the cell via overexpressed ABC transporter proteins. CTR1, copper ion transporter protein 1; OCT, organic cation transporters; GSH, glutathione; ROS, reactive oxygen species.

Intracellular GSH levels are modulated by various factors. Transforming growth factor β (TGF-β) is a well-known inhibitor of normal epithelial cell proliferation, and its suppression can increase the susceptibility of epithelial tissues to cancer. Interestingly, while high TGF-β signaling expression in the skin prevents benign papillary tumors from progressing to malignancy, it paradoxically facilitates the malignant transformation of squamous cell carcinoma stem cells into squamous carcinoma, thereby promoting metastasis (53). Upon activation, TGF-β ligands bind to TbRII, which phosphorylates TbRI. The activated TbRI then transmits signals by phosphorylating intracellular effectors SMAD2 and SMAD3 (SMAD2/3). These phosphorylated SMAD proteins form a complex with SMAD4, which interacts with other transcriptional regulators to activate downstream target genes. Notably, TGF-β reporter gene-positive basal cells exhibit high expression of genes involved in GSH metabolism and significantly lower ROS levels (53). In RNA-seq analysis of tyrosine kinase receptor inhibitor (TKI)-resistant non-small cell lung cancer, aldo-keto reductase 1B1 (AKR1B1) was found to be highly expressed in multiple drug-resistant cell lines, promoting GSH biosynthesis through STAT3-mediated upregulation of SLC7A11-dependent cystine uptake, leading to TKI resistance (54).

Both GSH and GST levels are elevated in tumor cells compared with normal cells, closely correlating with drug resistance. GSH levels can be measured using gold nanoparticles detected by a lateral flow plasma biosensor or even visually, with quantification achieved through automated analysis software. This method has shown a strong positive correlation between GSH levels and temozolomide resistance in GBM cells (55).

Beyond the GSH antioxidant system, eukaryotes possess another critical antioxidant mechanism-the thioredoxin system-which manages intracellular oxidative stress and supports cell proliferation when GSH is depleted (56). Cytosolic flavin adenine dinucleotide oxidoreductase 1 (TXNRD1), a selenoprotein with extensive antioxidant and redox regulatory functions, is overexpressed in numerous cancers and plays a key role in their growth and survival. Inhibiting TXNRD1, especially in the context of GSH depletion, increases oxidative stress within tumor cells, leading to their death (57). Given the protective role of the GSH system in shielding tumor cells from chemotherapeutic agents and ROS, exploring the regulatory mechanisms of this system and developing strategies to deplete GSH in tumor cells using molecularly targeted drugs or nanomaterials holds significant therapeutic promise.

Closure of nuclear pores and exocytosis of drugs in the nucleus. The nuclear pore complex is a basket-like structure embedded within the inner and outer nuclear membranes, featuring apertures of ~70-80 nm and a channel diameter of ~9 nm, facilitating the exchange of substances between the nucleus and the cytoplasm. Numerous chemotherapeutic agents, such as platinum and fluoropyrimidines, which inhibit DNA replication, must traverse the nuclear pore complex to reach their targets and exert their cytotoxic effects (58). Vault particles, barrel-shaped structures primarily composed of major vault protein (MVP), vADP-ribose polymerase, and telomerase-associated protein 1, are considered to interact with the nuclear pore complex. MVP, which constitutes 70% of the vault's mass, is considered to mediate the translocation of macromolecules, potentially rerouting chemotherapeutic drugs away from their subcellular targets and contributing to multidrug resistance in tumor cells (59,60). However, this hypothesis requires further validation.

Lung resistance-related protein (LRP), also known as major vault protein, is a key component of vault particles and nuclear pore complexes in humans (61). Studies have demonstrated that LRP is highly expressed in numerous tumor cells that lack P-gp expression, and its elevated levels are associated with reduced chemotherapy sensitivity (62). In a lung adenocarcinoma cell model, gefitinib-resistant cells exhibited

significant upregulation of YB-1, which promotes downstream AKT signaling and activates epithelial-mesenchymal transition (EMT), thereby increasing resistance to gefitinib through direct activation of MVP (63). CD73, a glycosylphosphatidylinositol-anchored plasma membrane protein, physiologically hydrolyzes extracellular adenosine monophosphate into adenosine and inorganic phosphate. Evidence suggests that CD73 interacts with MVP, activating the SRC-AKT pathway and affecting gemcitabine chemosensitivity in pancreatic ductal adenocarcinoma (64).

While LRP is known to enhance tumor cell resistance to chemotherapeutic agents, MVP deficiency has been associated with a reduced likelihood of tumor progression. In HBV-encoded protein X (HBx)-transgenic (TG) mice crossed with LRP-deficient mice, significant reductions in tumor number, size, liver-to-body weight ratio, alanine aminotransferase levels and alpha-fetoprotein levels were observed compared with HBx-TG mice carrying the HBx, indicating that LRP loss greatly diminishes tumor progression and extends survival time (65).

Vault RNAs (vtRNAs), non-coding RNAs comprising ~5% of vault particles, have been found to show high expression in cell lines with elevated EBV protein levels, particularly those expressing high levels of LMP1. Overexpression of vtRNAs has been associated with increased EBV expression and the inhibition of apoptosis through the overexpression of NOL3 and BCL-xl (59). Although most chemotherapeutic agents, including platinum compounds, antibiotics and phytochemicals, require nuclear entry to function effectively, the mechanisms governing their translocation across the nuclear membrane remain underexplored. Further investigation into the nuclear transport mechanisms of chemotherapeutic drugs and other macromolecules is essential for advancing the understanding of tumor chemoresistance.

Increased DNA repair. The DNA damage response (DDR) pathway plays a pivotal role in recognizing, signaling and repairing DNA damage caused by endogenous or exogenous factors, including chemotherapeutic agents. It also regulates cell cycle progression through DNA repair mechanisms, mitigating damage and preventing apoptosis in the case of unrepaired lesions. As such, the DDR pathway is a critical target in cancer therapy (66-68). Numerous chemotherapeutic drugs, such as platinum compounds, alkylating agents and antibiotics, induce DNA double-strand breaks by directly binding to DNA. These breaks are among the most lethal forms of DNA damage; failure to repair them triggers cell death. Enhanced DNA repair mechanisms are a key factor in the development of multidrug resistance in tumor cells (58,69-71).

Two primary pathways are responsible for repairing DNA double-strand breaks (DSBs): non-homologous end-joining (NHEJ) and homologous recombination (HR). HR typically requires sister chromatids as templates, limiting its activity to the S and G2 phases of the cell cycle. The efficiency of DNA repair largely depends on HR-promoting factors including BRCA1 and NHEJ-promoting proteins such as TP53BP1 (72). BRCA1 and BRCA2 are essential for repairing DSBs, playing a key role in inhibiting tumor cell proliferation and contributing to drug resistance (73-75). Cells with defective BRCA1 or BRCA2 genes exhibit reduced homologous recombination repair capacity, making them more sensitive to DNA-damaging agents such as cisplatin and poly (ADP-ribose) polymerase (PARP) inhibitors (75).

DNA topoisomerase-2 (TOP2) is an enzyme essential for DNA replication, transcription and recombination, with a known role in promoting cancer across various tumors (76). In hepatocellular carcinoma cells, continuous exposure to regorafenib leads to upregulation of TOP2A expression, while silencing TOP2A increases the sensitivity of these cells to regorafenib (77).

PARP, a poly ADP-ribose polymerase, is involved in chromatin modification, DNA replication, transcription and DNA repair, particularly through base excision repair of single-strand DNA (ssDNA) damage. In the absence of functional PARP, ssDNA breaks remain unrepaired, leading to DSBs during subsequent cell cycles as DNA replication forks encounter ssDNA regions. Cells with intact DSB repair pathways can repair such breaks and survive. PARP inhibitors (PARPi) specifically target BRCA1/2-deficient tumors, inducing apoptosis (73). BRCA1/2 mutant cells are particularly vulnerable to PARPi due to their inability to repair DSBs effectively (73). Treatment with the PARP inhibitor olaparib has been shown to restore sensitivity to conventional chemotherapy in patients with prostate cancer resistant to standard treatments and carrying defective DNA repair genes, such as BRCA1/2 (78).

The phosphatase and tensin homolog (PTEN) gene is critical in regulating DNA damage repair, chromosome stability and cell cycle progression through phosphatase-independent mechanisms. Phosphorylation at tyrosine 240 (pY240-PTEN) is frequently observed in patients with tumors undergoing radiotherapy. This phosphorylated form of PTEN is highly expressed, associates with chromatin via interaction with Ki-67, facilitates RAD51 recruitment, and enhances DNA repair processes, contributing to chemoresistance and poor prognosis (70).

Schlafen family member 11 (SLFN11) is another key regulator of DNA damage repair and is linked to the cellular response to DNA-damaging agents *in vitro*. Replication protein A (RPA), a heterotrimeric complex, is the primary eukaryotic single-stranded DNA-binding protein, crucial for various DNA metabolic pathways, including DNA replication, recombination, damage checkpoints and repair. SLFN11 is recruited to sites of DNA damage in an RPA-dependent manner, destabilizing the RPA-ssDNA complex. Elevated levels of SLFN11 result in defects in checkpoint maintenance and homologous recombination repair, thereby sensitizing cells to DNA-damaging agents (79). Enhancer of zeste homolog 2 (EZH2) induces the H3K27me3 histone modification, leading to the silencing of SLFN11 *in vivo*. The use of EZH2 inhibitors in combination with standard cytotoxic therapies has been identified to prevent secondary resistance and improve the efficacy of chemotherapy in both chemo-sensitive and chemoresistant small-cell lung cancer models (80).

Mutations in DNA methyltransferase 3A (DNMT3A), particularly at arginine 882 (DNMT3Amut), are commonly associated with poor response to erythromycin chemotherapy. DNMT3Amut cells exhibit impaired nucleosome expulsion and chromatin remodeling in response to anthracyclines, which in turn hinders the recruitment of the histone chaperone

SPT-16. This defect impairs the cell's ability to detect and repair DNA damage, exacerbating the DNMT3Amut phenotype. Additionally, DNMT3Amut cells display reduced CHK1 phosphorylation, along with diminished downstream p53 phosphorylation/stabilization and apoptotic signaling, further contributing to chemoresistance (81).

DNA mismatch repair (MMR) is a conserved process that identifies and corrects spontaneously misincorporated bases during DNA replication, ensuring genomic integrity (82). Impairment in MMR leads to microsatellite instability (MSI), a hallmark found in >20 different tumor types (82). Werner helicase (WRN), part of the RecQ family of DNA helicases, is critical in maintaining genomic stability, DNA repair, replication, transcription and telomere maintenance. WRN has been identified as a synthetic lethal target in deficient (d)MMR/MSI-H cancers, being essential for the survival of dMMR/MSI-H cells both *in vitro* and *in vivo*. Knockdown of WRN in these cells induces double-stranded DNA breaks and significant genomic instability, leading to apoptosis. WRN inhibition has proven effective in dMMR colorectal cancer models that develop secondary resistance to broad-spectrum chemotherapeutic agents such as irinotecan, oxaliplatin, or 5-FU, as well as combinations involving epidermal growth factor receptor (EGFR) monoclonal antibodies and BRAF or NTRK inhibitors (82).

While enhanced DNA repair can contribute to chemotherapy resistance, molecular alterations in MMR-related genes can also drive tumorigenesis and progression (83). Studies have revealed that cells exposed to targeted therapies (for example, EGFR inhibitors or BRAF inhibitors) temporarily downregulate the expression of DDR-related genes, including those involved in MMR and HR. This transient suppression of DDR capacity is reversible, with gene expression returning to normal levels after the cessation of targeted therapy (84). The presence of DNA damage and repair mechanisms within tumor cells-and whether these mechanisms are actively engaged to prevent apoptosis-presents a strategic opportunity for combination therapies. Exploiting the transient DDR deficiencies that tumors experience during treatment could enhance the effectiveness of anticancer therapies.

Effect of TME on chemotherapy resistance. The tumor microenvironment (TME) is characterized by several distinct features that differentiate it from normal tissues, including acidic pH, hypoxia, elevated ROS, upregulated antioxidant systems and overexpression of specific enzymes (47). Hypoxia, a hallmark of tumors, arises from the imbalance between oxygen consumption and vascular oxygen supply in tumor tissues and is a critical factor in promoting tumorigenesis and progression. This condition drives metabolic reprogramming in tumor cells, allowing them to adapt to the hypoxic TME (85). While platinum-based chemotherapeutic drugs target rapidly proliferating cancer cells, the quiescent cell population, often associated with hypoxia, remains largely unaffected by such treatments. Hypoxia-inducible factor 1 (HIF-1), composed of alpha and beta subunits, is a key regulator of cellular hypoxic responses. HIF-1α specifically modulates the cellular response to hypoxia, influencing processes such as apoptosis, proliferation, vasodilation, energy metabolism and angiogenesis. Salidroside has been identified to promote the degradation of HIF-1α, and its administration in combination with platinum drugs can reverse platinum resistance and inhibit metastasis induced by the hypoxic TME (86).

Hypoxia also contributes to tumor growth by affecting exosome secretion. Exosomes, nanoscale extracellular vesicles (30-150 nm in diameter), facilitate the transfer of proteins, RNA and other molecules between cells within the TME, thereby influencing the behavior of surrounding cells. In the context of EGFR-mutant lung cancer, a common target in clinical therapy, drug resistance remains a significant challenge. It has been demonstrated that cells with wild-type EGFR can be internalized by EGFR-mutant cancer cells via clathrin-dependent endocytosis, leading to the acquisition of a wild-type EGFR phenotype. This phenotypic change activates downstream PI3K/AKT and MAPK signaling pathways, thereby triggering drug resistance (87). Additionally, the EGFR-targeted drug oxitinib has been shown to promote exosome release by upregulating Rab GTPase, further contributing to drug resistance (87).

In acute myeloid leukemia (AML), the apoptosis repressor with caspase recruitment domain (ARC) protein serves as a potent independent marker of poor prognosis. ARC activates NF-κB, leading to increased IL1β expression in AML cells, which in turn elevates the expression of CCL2, CCL4 and CXCL12 in mesenchymal stromal cells (MSCs) (88). When AML cells are co-cultured with MSCs, IL1β expression is further elevated, driving AML cell migration towards CCL2, CCL4 and CXCL12. Inhibition of IL1β has been revealed to reduce AML cell migration (88). Moreover, co-cultures of AML and MSCs have been found to increase Cox-2 expression in MSCs through PGE2-mediated signaling in an ARC/IL1β-dependent manner, thereby modulating ARC expression and enhancing the chemoresistance of AML cells (89).

Microorganisms within the TME are significant contributors to cancer progression and treatment resistance. A study on ovarian epithelial cancer revealed that antibiotic use during chemotherapy was linked to poorer overall survival, primarily due to bacterial imbalance. Stool analysis indicated that co-treatment with antibiotics and cisplatin disrupted 49 non-resistant intestinal microbes in mice, leading to accelerated tumor growth and cisplatin resistance compared with mice treated with chemotherapy alone. This resistance was characterized by reduced apoptosis, increased DNA damage repair and enhanced angiogenesis. However, transplanting cecal microbes from control mice into the co-treated mice restored cisplatin sensitivity (90). Similarly, L-lactic acid produced by *Lactobacillus iners* in tumors reprograms cervical tumor metabolism, enhancing resistance to gemcitabine combined with 5-FU chemotherapy (91). *Fusobacterium nucleatum* and its metabolite succinic acid induce resistance to anti-PD-1 monoclonal antibody immune checkpoint blockade therapy in colorectal cancer by inhibiting key immune pathways and reducing $CD8^+$ T cell migration into the TME (92). In addition, telomelysin OBP-301, a telomerase-specific, replication-competent oncolytic adenovirus with an hTERT promoter upstream of the E1 gene, has been demonstrated to enhance Akt phosphorylation in hepatocellular carcinoma cells. However, the histone deacetylase inhibitor AR42 reduces telomerase-induced Akt phosphorylation and

enhances telomerase-induced apoptosis. Combined treatment with telomelysin and AR42 demonstrated synergistic anti-hepatocellular carcinoma effects (93).

Tumor cells do not exist in isolation; their characteristics are intricately linked to the TME. The interactions between tumor cells and other cells, including bacteria within the microenvironment, as well as the unique pH and hypoxic conditions, profoundly influence tumor cell characteristics and drug sensitivity. Inflammation within the TME promotes drug resistance by activating pro-inflammatory cytokines and signaling pathways. This chronic inflammatory response not only drives tumor growth and metastasis but also significantly reduces cancer cell sensitivity to chemotherapy through the regulation of resistance protein expression (94). Investigating how the microenvironment contributes to chemotherapy resistance may provide new therapeutic strategies that focus on targeting the TME, rather than the tumor cells alone.

4. Tumor cells escape from the pressure of chemotherapy through dormancy

What is tumor cell dormancy? Tumor recurrence years after chemotherapy or surgery is often attributed to the presence of dormant cancer cells within the tumor mass. Dormancy refers to a reversible state in which cells cease division, exhibit low metabolic activity, and reduce mRNA synthesis, yet remain responsive to external stimuli (95-97). Dormancy can occur in early metastatic sites as well as in residual lesions following chemotherapy (98-100). Traditionally, cellular dormancy was viewed as a quiescent state associated with the G0 phase of the cell cycle (101). However, it was recently suggested that these non-dividing cells exist in a slow-cycling survival mode, akin to embryonic stasis, and are therefore also known as slow-cycling or drug-resistant persister cells (100).

Dormant tumor cells differ from tumor stem-like cells, though there is overlap between the two. Tumor stem-like cells are generally considered a subset of dormant tumor cells, possessing the ability to remain dormant, yet not all dormant cells possess stem cell properties such as self-renewal and differentiation.

Most chemotherapeutic agents target proliferating cells, allowing tumor cells to evade therapeutic stress by entering a dormant state, thereby contributing to drug resistance (102,103). Although some reactivated cells may remain sensitive to chemotherapy, the prognosis for patients with recurrent tumors is often poor (100,104). The induction of dormancy in response to drug treatment underscores the importance of accurately identifying dormant tumor cells to improve guidance of clinical drug use (105).

How to determine tumor cell dormancy. Next-generation sequencing and lentiviral barcoding experiments have revealed that xenograft tumors arising after chemotherapy-induced dormancy do not exhibit significant reductions in genetic or barcode complexity, indicating that dormancy is a non-genetic state (100). Tumor cell dormancy functions as a survival strategy, enabling cells to adapt to external stress rather than representing a distinct subpopulation; all tumor cells have the potential to enter a dormant state (100). Currently, there are no specific markers for identifying dormant tumor cells. Detection primarily relies on immunohistochemistry, immunofluorescence and western blot analysis of relevant indicators, typically associated with tumor stem-like cells, such as CK, Sox-2 and CD133, as well as dormancy activation markers including Ki-67, cyclin D1, C-myc, VEGF and proliferating cell nuclear antigen. TUNEL staining is also commonly used (106). Additionally, tracking the mitotic kinetics of dormant tumor cells with lipophilic fluorescent dyes serves as another method for determining cellular dormancy (107). One of the key features of dormant cells is reduced mRNA synthesis activity. Since mRNA is transcribed by RNA polymerase II (RNApII), low RNApII phosphorylation is highly specific to dormant cells, with cyclin-dependent kinase 9 (CDK9) being critical for RNApII-dependent gene transcription. The Optical Stem Cell Activity Reporter system distinguishes dormant cells from proliferating cells by detecting intracellular transcriptional status (95). *In vitro* immobilization techniques can also be employed to isolate and recover dormant cancer cells. This can be achieved using a microfluidic flow-focusing device that allows individual cells coated with agarose to be immobilized and survive on silica gel wells. Typically, actively proliferating cells do not survive the immobilization process, but dormant cells can be re-awakened by *in situ* digestion of the agarose gel and effectively recovered through magnetic separation of the silica gel (108) (Fig. 4).

Mechanisms of tumor cell dormancy. In breast cancer, the tyrosine kinase receptor TIE2 induces cell dormancy and resistance to 5-FU and adriamycin by activating the expression of cyclin-dependent kinase inhibitors CDKN1A and CDKN1B (109). The treatment of diabetes with metformin or a high-fat diet can promote the survival of dormant ER^+ breast cancer cells through the upregulation of the AMPK signaling pathway and the activation of fatty acid oxidation (105). FBX8, a member of the F-box protein family, plays a role in maintaining tumor cell dormancy under the pressure of chemotherapy with drugs such as oxaliplatin and 5-FU. Overexpression of FBX8 in dormant cells enhances the degradation of HIF-1α, CDK4 and C-Myc via the ubiquitin-proteasome pathway, thereby prolonging the dormancy period, whereas FBX8 knockdown shortens this period (106). In paclitaxel-treated non-small cell lung cancer, regulator of G protein signaling 2 (RGS2) mediates translational arrest and dormancy in tumor cells through the proteasomal degradation of activating transcription factor 4, while antagonizing RGS2 in the endoplasmic reticulum pathway induces apoptosis in dormant cells (110). CXCL10 has been identified as a factor that can reactivate the proliferation of dormant tumor cells within micro-metastases, making it a potential therapeutic target for addressing tumor dormancy (111). Elevated intracellular copper levels are generally associated with tumor progression; however, copper carrier drugs such as elesclomol can induce cell death in a copper-ion-dependent manner. Consequently, blocking copper uptake can inhibit tumor cell proliferation and induce dormancy, reducing overall cell mortality (112,113).

The MAPK/ERK signaling pathway, a classical proliferation-related pathway, also plays a role in the induction of cell dormancy. In EGFR-mutated non-small cell lung cancer, the combination of EGFR inhibitors and TKIs drives tumor cells into a senescence-like dormant state characterized by high

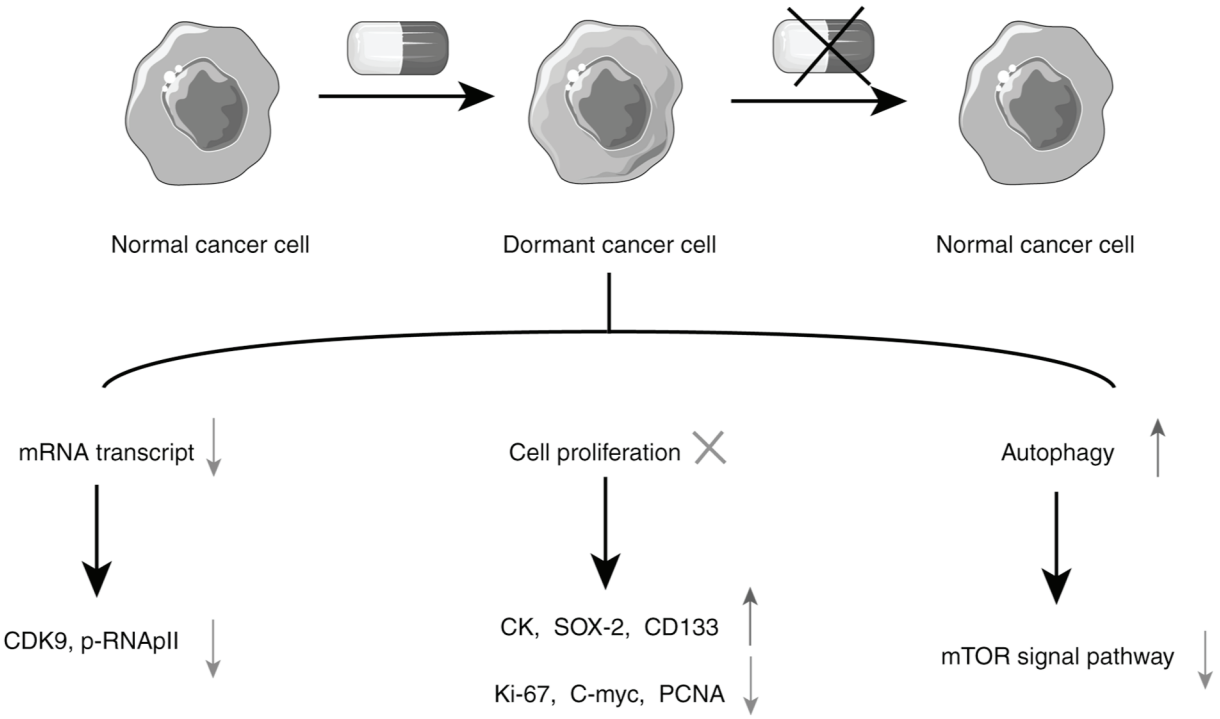

Figure 4. Tumor cells entering dormancy to evade chemotherapy: In response to chemotherapeutic stress, tumor cells can enter a slow-cycling, non-dividing state known as dormancy, allowing them to evade the effects of drugs that target actively dividing cells. Dormant cells are characterized by halted cell division, reduced mRNA transcription and increased autophagy. Once the external chemotherapeutic pressure is lifted, these dormant tumor cells can reactivate and resume proliferation. PCNA, proliferating cell nuclear antigen.

YAP/TEAD activity, owing to ERK1/2 blockade. Inhibiting YAP and TEAD in conjunction with EGFR/MEK inhibition has been shown to enhance apoptosis, effectively depleting dormant cells (114).

Myc is a critical gene that regulates tumor cell growth and proliferation. Inhibition of Myc or bromodomain-containing protein 4 prompts tumor cells to enter dormancy by reducing the initiation of apoptosis. Conversely, inducing Myc expression increases chemotherapy sensitivity, suggesting that maintaining dormancy through Myc inhibition post-chemotherapy or disrupting dormancy by inhibiting CDK9 could be promising therapeutic strategies against dormant tumor cells (115).

Autophagy plays a pivotal role in cellular stress response by eliminating damaged organelles, misfolded proteins and abnormal protein aggregates, regulating mitochondrial mass, and preventing the accumulation of ROS, thereby aiding cell survival (102). Studies have revealed that when tumor cells enter a dormant state, the activity of the autophagy-related mTOR pathway decreases, while autophagy-associated phenotypes increase (102,116). Conversely, inhibiting autophagy with drugs such as chloroquine can reawaken dormant cells, prompting them to re-enter the proliferative state (117). The combination of autophagy inhibitors with chemotherapeutic agents has been found to induce the death of dormant cells (100,118). Thus, autophagy is integral not only to the initiation and maintenance of dormancy but also to the transition from dormancy to proliferation.

The TME significantly contributes to inducing tumor cell dormancy. In a mouse model of breast cancer metastasis, Ki-67 immunofluorescence revealed that tumor cells metastasizing to the lungs entered a dormant state. This metastatic dormancy was dependent on the presence of T cells, particularly $CD39^{+}PD\text{-}1^{+}CD8^{+}$ T cells, which induced cell cycle arrest by secreting IFNγ and TNF-α, thereby promoting a dormant phenotype (119). Hypoxia, another key feature of the TME, also influences dormancy. Under hypoxic conditions, the expression of CSN8, a subunit of the COP9 signalosome, is elevated. This upregulation is accompanied by increased levels of dormancy markers (NR2F1, DEC2 and p27) and hypoxia markers (HIF-1α and GLUT1), along with decreased expression of the proliferation marker Ki-67, suggesting that CSN8 plays a role in regulating hypoxia-induced dormancy (120).

While most chemotherapeutic agents target proliferating cells and are ineffective against dormant cells, nimustine has shown efficacy in targeting dormant cells in BRCA1-deficient mice. Platinum-induced intra-strand crosslinks can be repaired by nucleotide excision during the G0-G1 phase; however, in BRCA1-deficient tumor cells, nimustine-induced inter-strand crosslink repair is impaired, leading to cell death (98).

The study of tumor cell dormancy and its role in chemotherapy resistance remains an emerging field. The definitions, markers and specific mechanisms of tumor cell dormancy remain incompletely understood. However, continued research is essential to elucidate how tumor cells evade chemotherapy and survive as micro-metastases, ultimately improving therapeutic strategies.

5. Conclusion and future directions

In recent decades, the molecular mechanisms underlying chemoresistance have become increasingly well-understood.

These mechanisms include reduced drug uptake into cells, increased drug efflux, GSH-mediated drug neutralization, nuclear pore closure, enhanced DNA repair, promotion of tumor cell dormancy, and the complex interactions between tumor cells and the TME. Although the mechanisms underlying chemotherapy resistance in tumor cells are increasingly well understood, their complexity in clinical practice presents significant challenges. For example, the use of inhibitors targeting multidrug resistance transporter proteins such as MDR1 is complicated by their role in immune function. Literature indicates that $CD8^+$ T cells secrete various cytokines to mediate immune responses and exert cytotoxic effects on viruses and tumor cells, processes in which MDR1 plays a critical role. MDR1 is essential for the development of naive $CD8^+$ T cells, regulated primarily by Runt-Related transcription factors, which help inhibit oxidative stress, enhance cell survival, and protect the mitochondrial function of nascent $CD8^+$ cytotoxic T lymphocytes. Therefore, inhibiting MDR1 in patients with cancers could impair immune function, potentially leading to treatment failure (121).

The development of nanomaterials designed to deliver chemotherapeutic agents directly to specific tumor sites or intracellular targets is a rapidly expanding area of research aimed at reversing chemoresistance. For example, a nanomaterial containing an iron oxide core has been engineered to deliver the cytotoxic agent adriamycin and the TLR3 agonist polyinosinic: Polycytidylic acid (Poly IC) to both breast cancer and dendritic cells. The Endoglin-binding peptide on the nanomaterial targets triple-negative breast cancer cells, inducing apoptosis through multiple mechanisms, thereby inhibiting tumor growth and metastasis. This approach has shown significant success in prolonging the survival of mouse models with aggressive and resistant triple-negative breast cancer metastases (122). Current strategies to combat GSH-mediated cellular resistance focus on GSH depletion or targeting GST. For instance, ethacraplatin, a platinum prodrug, inhibits GST by releasing ethacrynic acid, and encapsulating this compound in nanomicelles has been identified to enhance the intracellular accumulation of cisplatin (123).

Some polysulfides have been developed to target high GSH levels in tumor cells, serving as a prodrug backbone that also reverses multidrug resistance (5,124). Additionally, nanocarriers such as dendritic mesoporous silica nanoparticles can integrate components such as ultrasmall Fe_3O_4 nanoparticles, Mn^{2+} ions and the glutaminase inhibitor Telaglenastat (CB-839) into their large mesopores to form nanodrugs. These nanodrugs exhibit peroxidase-mimetic activity under acidic conditions, catalyzing the decomposition of hydrogen peroxide (H_2O_2) into hydroxyl radicals (-OH) and depleting existing GSH while blocking endogenous GSH synthesis. This process enhances ROS-mediated tumor catalytic therapy (125). Given the ongoing challenges with traditional inhibitors in combating chemotherapy resistance, the development of new nanomaterials represents a promising strategy for overcoming multidrug resistance in tumors, and it is expected to be a key focus of future research.

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Availability of data and materials

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Authors' contributions

XW and WHZ conceived and designed the analysis, conducted the research, and drafted the manuscript. LHX created the figures. LYZ and PL contributed to the revision and polishing of the manuscript. ZL, WJG, QQ, DLC and XZ were involved in the conception and design of the analysis. XZ made significant contributions to the discussion of the content and reviewed, edited and finalized the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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