Mechanism of Chemotherapy Resistance: a Comprehensive Review

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Abstract
Chemotherapy resistance is a critical barrier to effective cancer treatment, contributing to the high number of cancers related death in patients. This review comprehensively examines the molecular mechanisms driving resistance, including innate and acquired resistance, tumor heterogeneity, and tumor microenvironment (TME) interactions. Key mechanisms include enhanced drug efflux via ABC transporters, increased DNA repair, altered drug targets, drug detoxification, and evasion of apoptosis. Tumor heterogeneity fosters resistant subclones, while TME factors like hypoxia and cancer-associated fibroblasts (CAFs) exacerbate resistance. Crosstalk between signaling pathways, such as PI3K/AKT and MAPK, fuels resistance but offers hope for combination therapies. Insights into these mechanisms are vital for developing targeted therapies to overcome resistance and improve patient outcomes.

Keywords: Cancer, Chemotherapy Resistance, Multidrug Resistance, Signaling Cross-Talk, Tumor Heterogeneity, Tumor Microenvironment

Introduction
Cancer is a disease marked by the uncontrolled growth and spread of abnormal cells, which can form tumors, invade nearby tissues, and metastasize to distant organs via the blood or lymphatic systems. According to global estimates, it remains the second leading cause of death, with 19.3 million new cases and 10 million cancer-related deaths reported in 2020.[1,2] Treatment options vary based on cancer type and stage and may include surgery, chemotherapy, radiation, immunotherapy, therapy, and stem cell transplants.[3] Among these, chemotherapy plays a central role by targeting rapidly dividing cells. However, its effectiveness is often undermined by the development of drug resistance, which affects up to 70% of patients undergoing treatment.[4,5] Resistance may be present before therapy begins (innate) or may develop over time (acquired).[6] As a result of this heterogeneity, the bulk tumour might include a diverse collection of cells distinct molecular signatures with differential levels of sensitivity to treatment. This heterogeneity might result in a non-uniform distribution of genetically distinct tumour-cell subpopulations across and within disease sites spatial heterogeneity. This review aims to provide a comprehensive overview of the key molecular and cellular mechanisms behind chemotherapy resistance, offering insights that may inform the development of more tailored and effective treatment strategies.

Mechanism of Chemotherapy Resistance
Innate resistance
Innate, or intrinsic, resistance refers to the natural, pre-existing capacity of cancer cells to withstand the effects of chemotherapy before any treatment has begun. This resistance is often driven by genetic and molecular alterations, activation of intrinsic survival pathways, and tumor heterogeneity, all of which contribute to reduced drug sensitivity [9,10]. One well-documented mechanism involves the overexpression of ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp; encoded by ABCB1), which actively expel chemotherapeutic agents from the intracellular space. For instance, increased expression of ABCB1 has been observed in lung and breast cancers, contributing to resistance against drugs like doxorubicin.[11,12] Additionally,

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mutations in key genes such as TP53 compromise the cell's ability to respond to DNA damage, thereby enabling continued proliferation despite genotoxic stress.[13,14]

Disruption of apoptosis is another central feature of innate resistance. Apoptosis is regulated by two primary pathways: intrinsic (mitochondria-mediated) and (death receptor-mediated).[15] The Bcl-2 protein family plays a critical role in this process and includes both pro-apoptotic (e.g., Bax, Bak, Bad, Bok) and anti-apoptotic (e.g., BCL-2, BCL-xL, MCL-1) members.[16,17] In many hematologic malignancies, overexpression of anti-apoptotic proteins such as BCL-2 and BCL-xL has been associated with resistance to therapy by inhibiting the programmed cell death that chemotherapy is designed to induce.[18,19] Another layer of complexity arises from tumor heterogeneity—the presence of genetically and phenotypically distinct subpopulations within the same tumor. This variability can be intratumoral, intermetastatic, or intrametastatic in nature.[20] Such diversity allows some subclones to inherently resist treatment, while others may initially respond but later contribute to relapse due to selective pressure imposed by chemotherapy.[7, 21–23]

Acquired resistance

Acquired resistance develops progressively during the course of chemotherapy as cancer cells undergo adaptive molecular and phenotypic changes that enable them to evade the cytotoxic effects of treatment. This resistance is multifactorial, involving a range of mechanisms that collectively diminish the therapeutic efficacy of anticancer agents.

A. Release of drug outside the cell (Drug Efflux

One of the most studied mechanisms of acquired resistance is the increased efflux of drugs from cancer cells. Members of the ATP-binding cassette (ABC) transporter family—particularly P-glycoprotein (ABCB1/MDR1), multidrug resistance-associated proteins (ABCC/MRP), and breast cancer resistance protein (ABCG2/BCRP)—actively transport a wide range of chemotherapeutic agents across the plasma membrane, thereby reducing their intracellular accumulation.[24, 25] These transporters are frequently overexpressed in drug-resistant cancers, including ovarian and colorectal malignancies, and contribute to resistance against agents such as paclitaxel, vincristine, and mitoxantrone.[26–28] Beyond these well-characterized proteins, other ABC transporters have also been implicated in mediating resistance through similar drug efflux mechanisms.[24]

B. Enhance DNA repair activity

A key strategy for cancer cells to adapt and survive within the body against drugs is to enhance their DNA repair mechanisms significantly. Chemotherapy-induced DNA damage is counteracted by enhanced DNA repair mechanisms, including homologous recombination (HR), non-homologous end joining (NHEJ), and base excision repair (BER).[29,30] The expression of repair protein such as AP endonuclease1 (APE1), Poly (ADP-ribose) polymerase (PARP), and DNA-dependent protein kinase (DNA-PK), can render cancer cells resistant to specific chemo-radiotherapeutic agents. For instance, APE1 and PARP facilitate repair of alkylating agent-induced damage, while high levels of DNA-PK contribute to chemo-radiotherapy resistance by efficiently rejoining double-strand breaks.[31,32] Similarly, Overexpression of repair proteins like RAD51 or O-6-methylguanine-DNA methyltransferase (MGMT) promotes resistance to alkylating agents like temozolomide in glioblastoma and other solid tumors.[33,34] Mutations in DNA damage response genes, such as ATM or BRCA1/2, further contributed to enhanced repair capacity, limiting the cytotoxic effects on DNA targeting agents.[35,36]

C. Alteration of target sites.

Mutations in drug target sites or changes in receptor expressions reduce binding affinity, leading to resistance.

A prime example is the mutation in the kinase domain of the fusion gene BCR-ABL in Chronic Myeloid Leukemia (CML) cause imatinib resistance, the first FDA-approved tyrosine kinase inhibitor (TKI).[37,38] Initially it was believed to be a game changer, significantly increasing 10-year survival rates from 50% to approximately 80% of patients with chronic-phase CML (38,39). Despite its initial success, after a few years, about 20% to 30% of patients experienced resistance or relapse due to a mutation occurring in threonine 315 to isoleucine.[40] To overcome this resistance, the next generation of TKIs has been discovered, including Nilotinib, dasatinib, bosutinib, and ponatinib.[39,41,42] Addtionally, In

non-small-cell lung cancer (NSCLC), the EGFR T790M mutation hinders binding of tyrosine kinase inhibitors (TKIs) like gefitinib, necessitating the use of third-generation TKIs like osimertinib.[43,44]

D. Expression of detoxification of drugs

Numerous chemotherapeutic agents are governed by drug-metabolizing enzymes: Phase I enzymes such as cytochrome P450 (CYP family proteins), and Phase II, which includes glutathione S-transferases (GSTs) and UDP-glucuronosyltransferases (UGTs).[45,46] Malfunctioning and overexpression of these enzymes and related metabolic pathways can lead to drug detoxification or the failure to convert drugs into their active forms, constituting significant challenges in cancer treatment.[47,48] For example, CYP3A4 metabolizes irinotecan into inactive forms in colorectal cancer, while GSTs reduce the cytotoxicity of agents like cisplatin through conjugation reactions.[46,49] Overexpression of UDP-glucuronosyltransferases (UGT1A1) detoxifies SN-38, the active metabolite of irinotecan, further contributing to resistance.[50]

E. Impaired Apoptotic Response and Autophagy Activation

The ability of cancer cells to evade apoptosis is a hallmark of chemoresistance. Overexpression of anti-apoptotic BCL-2 family proteins (e.g., BCL-2, MCL-1) stabilizes the mitochondria, preventing cytochrome c release and subsequent caspase activation.[15,51] Similarly, reduced expression of death receptors like FAS/CD95 impairs extrinsic apoptosis, as observed in certain resistant lymphomas.[52] Like apoptosis, autophagy also regulates cell survival by degrading damaged or unnecessary cellular components, thus maintaining homeostasis and preventing malignant transformation. However, its role is paradoxical: while autophagy suppresses tumorigenesis in early stages, it supports cancer progression in later stages by supplying energy under hypoxia, nutrient deprivation, and cellular stress. In ovarian cancer, for instance, cisplatin-induced autophagy reduces drug efficacy, whereas autophagy inhibitors like chloroquine enhance cytotoxicity.[53,54]

Tumor Heterogeneity mediated drugs resistance

Tumor heterogeneity is a defining characteristic of most malignancies and poses a major challenge to effective chemotherapy. It encompasses the coexistence of diverse subpopulations of cancer cells within a single tumor (intratumor heterogeneity) or among metastatic sites (intertumor and intrametastatic heterogeneity). These subclones differ genetically, epigenetically, and phenotypically, resulting in variable responses to treatment.[55,56] This diversity enables certain subpopulations to withstand chemotherapeutic pressure while others may initially respond but later develop resistance. These resistant clones can expand under the selective pressure of treatment, ultimately driving disease progression and relapse.[7,57] For example, within a single breast tumor, HER2-positive and HER2-negative subclones may exhibit differential sensitivity to trastuzumab, complicating targeted therapy responses.[58] Mechanistically, heterogeneity manifests in several resistance-related features, such as upregulated efflux pumps, altered DNA repair capacity, and differences in apoptotic thresholds. Furthermore, studies have demonstrated that the evolutionary dynamics of tumors—marked by branching clonal evolution and subclonal expansion—are strongly associated with chemoresistance. Dentro et al. (2021) reported that over 90% of tumors across 38 cancer types showed evidence of subclonal diversification.[59] Clinical evidence further supports this concept. For instance, Kim et al. (2018) observed the persistence of resistant subclones in 10 out of 20 triple-negative breast cancer (TNBC) patients following neoadjuvant chemotherapy.[60] Similarly, Sheriff et al. (2021) reported a relapse rate of 77% in glioblastoma patients after RT-TMZ treatment, underscoring the role of pre-existing and therapy-induced resistant clones.[61]

Taken together, tumor heterogeneity significantly complicates therapeutic outcomes by allowing the survival and expansion of drug-resistant subpopulations. Addressing this challenge will require a more personalized, adaptive treatment approach that accounts for clonal diversity within tumors.

Tumor Microenvironment (TME) mediated drug resistance

The tumor microenvironment (TME) represents a complex and dynamic network of cellular and non-cellular components that significantly influence cancer progression and treatment outcomes. This

microenvironment consists of immune cells (e.g., macrophages, T cells, and natural killer cells), stromal cells such as cancer-associated fibroblasts (CAFs), extracellular matrix (ECM) proteins (e.g., collagen, fibronectin, hyaluronic acid), and soluble factors including cytokines and growth factors.[62,63] Together, these elements create a milieu that promotes tumor survival, immune evasion, and notably, resistance to chemotherapy. One of the key features of the TME is hypoxia, a state of outpaced oxygen and nutrient availability resulting from rapid tumor growth and outpacing angiogenesis.[62] Such adverse environments inside, manipulates the host cellular system for own shake, which ultimately fosters tumor progression, and promotes drug resistance. Hypoxic condition which is regulated by hypoxia-inducible factors (HIF-1α, HIF-2α), contribute to chemoresistance by the drug penetration, promoting metabolic reprogramming, and reducing oxidative stress, which is necessary for the efficacy of drugs such as doxorubicin [(64,65)]a phenomenon common in a majority of malignant tumors. Tumor-hypoxia leads to advanced but dysfunctional vascularization and acquisition of epithelial-to-mesenchymal transition phenotype resulting in cell mobility and metastasis. Hypoxia alters cancer cell metabolism and contributes to therapy resistance by inducing cell quiescence. Hypoxia stimulates a complex cell signaling network in cancer cells, including the HIF, PI3K, MAPK, and NFκB pathways, which interact with each other causing positive and negative feedback loops and enhancing or diminishing hypoxic effects. This review provides background knowledge on the role of tumor hypoxia and the role of the HIF cell signaling involved in tumor blood vessel formation, metastasis, and development of the resistance to therapy. Better understanding of the role of hypoxia in cancer progression will open new windows for the discovery of new therapeutics targeting hypoxic tumor cells and hypoxic microenvironment. The role of immune cells in the TME is indeed complex and often contradictory. Macrophages (TAMs), one of the major immune cell types found in the TME, exhibit diverse functions. While some M1 macrophages act as tumor suppressors with anti-inflammatory properties, M2 macrophages often take on a pro-tumorigenic role.[66] Several study notable reported that M2 macrophages suppress anti-tumor immune response, promote angiogenesis, and enhancing resistance to sorafenib in hepatocellular carcinoma[67], doxorubicin in TNBC [68], paclitaxel in BC[69]. Similarly, CAFs—fibroblasts that have undergone transformation within the tumor context—play a pivotal role in shaping the TME. They support tumor growth by secreting ECM proteins and soluble mediators, contributing to drug resistance by modifying drug delivery pathways and activating survival signaling in cancer cells[71,72]. CAF-mediated resistance has been observed with a range of therapies, including immune checkpoint blockade in metastatic bladder, melanoma, and kidney cancers; taxane resistance in prostate cancer; cisplatin resistance in non-small-cell lung cancer (NSCLC); and tamoxifen resistance in breast cancer[73–76]. These findings underscore the significance of the TME as not just a passive background but an active contributor to therapy failure. Targeting the supportive roles of CAFs, TAMs, and hypoxia-driven signaling pathways offers a promising strategy to overcome resistance and improve treatment efficacy.

Targeting Signaling Pathway Crosstalk: A bane or Boon to Chemotherapy treatment

Crosstalk between signaling pathways is a major driver of chemotherapy resistance, acting as a bane by enabling cancer cells to evade treatment through compensatory mechanisms. Notably, key pathways such as PI3K/AKT, MAPK/ERK, NF-κB, Wnt/β-catenin, and STAT3 often function in a coordinated manner, enhancing cellular defense mechanisms against cytotoxic agents. For example, activation of the PI3K/AKT pathway can upregulate ATP-binding cassette (ABC) transporters such as P-glycoprotein (P-gp), promoting drug efflux in breast cancer cells.[11,12] Similarly, Wnt/PI3K signaling has been shown to induce overexpression of RAD51, a critical DNA repair protein that contributes to chemoresistance in glioblastoma.[33] Crosstalk with NF-κB can promote apoptosis evasion through upregulation of anti-apoptotic proteins like BCL-2, further diminishing chemotherapy efficacy.[51] In the context of non-small-cell lung cancer (NSCLC), resistance to EGFR-targeted therapies is often mediated by compensatory activation of alternative pathways such as MET or PI3K/AKT. In particular, the EGFR T790M mutation, which emerges in up to 70% of patients treated with first-generation EGFR

inhibitors, leads to activation of downstream pathways that bypass EGFR blockade. This necessitates the use of next-generation agents such as osimertinib and MET inhibitors.[43,44] Tumor heterogeneity further complicates pathway targeting, as distinct subclones may rely on different signaling circuits. For instance, within a heterogeneous breast tumor, HER2-positive subclones may activate MAPK/ERK, while HER2-negative subclones depend on PI3K/AKT for survival, resulting in differential drug responses.[58] The tumor microenvironment also plays a role in reinforcing crosstalk-mediated resistance. CAFs and TAMs within the TME secrete cytokines such as TGF-β and IL-6, which activate survival pathways like PI3K/AKT and STAT3 in cancer cells. These interactions promote epithelial-to-mesenchymal transition (EMT), immune evasion, and resistance to agents such as cisplatin and 5-fluorouracil.[77,78]

Conversely, targeting signaling pathway crosstalk offers a boon for overcoming chemoresistance, providing opportunities for novel therapies. Combination therapies that simultaneously inhibit multiple pathways have demonstrated improved outcomes. For instance, co-administration of PI3K and MEK inhibitors (e.g., idelalisib and trametinib) has restored doxorubicin sensitivity in breast cancer models.[12] In NSCLC, combining osimertinib with MET inhibitors such as crizotinib has shown promising response rates in patients with EGFR T790M mutations.[44] Furthermore, emerging therapeutic strategies targeting the TME such as TGF-β inhibitors (e.g., galunisertib) and autophagy inhibitors (e.g., chloroquine)—have been effective in disrupting TME-induced signaling crosstalk and enhancing chemotherapy efficacy.[53,54,75,77] Precision medicine approaches, including single-cell sequencing, are increasingly being used to map signaling interactions and tailor therapies to individual patients, yielding improved outcomes in resistant breast cancers.[58,59] Collectively, these findings highlight the dual nature of signaling pathway crosstalk in chemoresistance as both a mechanism of resistance and a promising therapeutic.

Conclusion

Chemotherapy resistance remains a significant barrier in the management of cancer, contributing to therapeutic failure in over 70% of patients with advanced disease. Both innate and acquired mechanisms ranging from enhanced drug efflux, improved DNA repair, altered drug targets, and drug detoxification, to apoptosis evasion collectively compromise treatment efficacy. These molecular defenses are further compounded by tumor heterogeneity, which facilitates the survival of resistant subclones, and by the tumor microenvironment (TME), which creates a protective niche through hypoxia, immune modulation, and stromal interactions. Signaling pathway crosstalk, particularly among the PI3K/AKT, MAPK, NF-κB, and Wnt/β-catenin pathways, not only promotes resistance but also offers strategic targets for combination therapies. Efforts to disrupt this crosstalk alongside modulation of the TME and tailored, patient-specific approaches are central to overcoming chemoresistance. Future research should continue to explore integrated therapeutic strategies that account for both tumor-intrinsic adaptations and extrinsic environmental factors, thereby enhancing response rates and improving patient survival outcomes.

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