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DRUG RESISTANCE MECHANISMS IN CANCER: GENETIC AND EPIGENETIC DRIVERS

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ABSTRACT

Drug resistance represents a major obstacle in cancer treatment, contributing to therapeutic failure and disease recurrence. This review examines the molecular mechanisms underlying resistance to chemotherapy and targeted therapies, focusing on genetic alterations, epigenetic reprogramming, and cellular plasticity. Genetic drivers include mutations in oncogenes and tumour suppressor genes, amplification of drug efflux transporters, and alterations in DNA repair machinery. Epigenetic mechanisms encompass DNA methylation, histone modifications, and chromatin remodelling that collectively modulate drug sensitivity. Cell plasticity enables phenotypic transitions between drug-sensitive and resistant states through epithelial-mesenchymal transition and cancer stem cell characteristics. The tumour microenvironment further contributes to resistance through immunosuppression, metabolic reprogramming, and physical barriers to drug delivery. Understanding these multilevel mechanisms is crucial for developing combination therapies that can overcome or prevent resistance. This review synthesises current knowledge on resistance mechanisms and discusses emerging therapeutic strategies targeting these pathways.

KEYWORDS: Cancer drug resistance, genetic mutations, epigenetic modifications, cell plasticity, ABC transporters, DNA repair.

INTRODUCTION

Cancer remains one of the leading causes of mortality worldwide, with drug resistance emerging as the primary barrier to successful treatment outcomes. Despite remarkable advances in cancer therapeutics, including targeted therapies and immunotherapies, the majority of patients eventually develop resistance, leading to disease progression and therapeutic failure.[1] Drug resistance can be classified as intrinsic (pre-existing before treatment) or acquired (developing during therapy), with both mechanisms involving complex molecular alterations at genetic, epigenetic, and cellular levels.[2,3]

The development of resistance is fundamentally an evolutionary process driven by tumour heterogeneity and selective pressure from therapeutic interventions. Cancer cells harbour extensive genetic and epigenetic diversity, creating subpopulations with varying drug sensitivities.[4]. Treatment acts as a selective force, eliminating sensitive cells while allowing resistant clones to proliferate and

dominate the tumour mass. This Darwinian selection process is further complicated by the dynamic nature of epigenetic modifications and cellular plasticity, which enable rapid adaptation to therapeutic stress without requiring permanent genetic changes.[5,6]

Understanding resistance mechanisms is essential for developing effective combination therapies and treatment strategies. This review focuses on three major categories of resistance drivers: genetic alterations, epigenetic reprogramming, and cell plasticity, while also considering the critical role of the tumour microenvironment in facilitating resistance.

Genetic Mechanisms of Drug Resistance

Mutations in Drug Targets

Target gene mutations represent a primary mechanism of acquired resistance to targeted therapies. Cancer cells can acquire point mutations, insertions, or deletions in genes encoding therapeutic targets, reducing drug binding affinity or abolishing target function altogether.[7] In non-small cell lung cancer (NSCLC), EGFR T790M gatekeeper mutation emerges in approximately 50-60% of patients treated with first-generation EGFR tyrosine kinase inhibitors (TKIs), sterically hindering drug binding while maintaining kinase activity.[8] Similarly, ABL kinase domain mutations, particularly T315I, confer resistance to imatinib in chronic myeloid leukemia by preventing inhibitor binding to the ATP-binding pocket. Figure 1 presents the Multilevel mechanisms of cancer drug resistance.

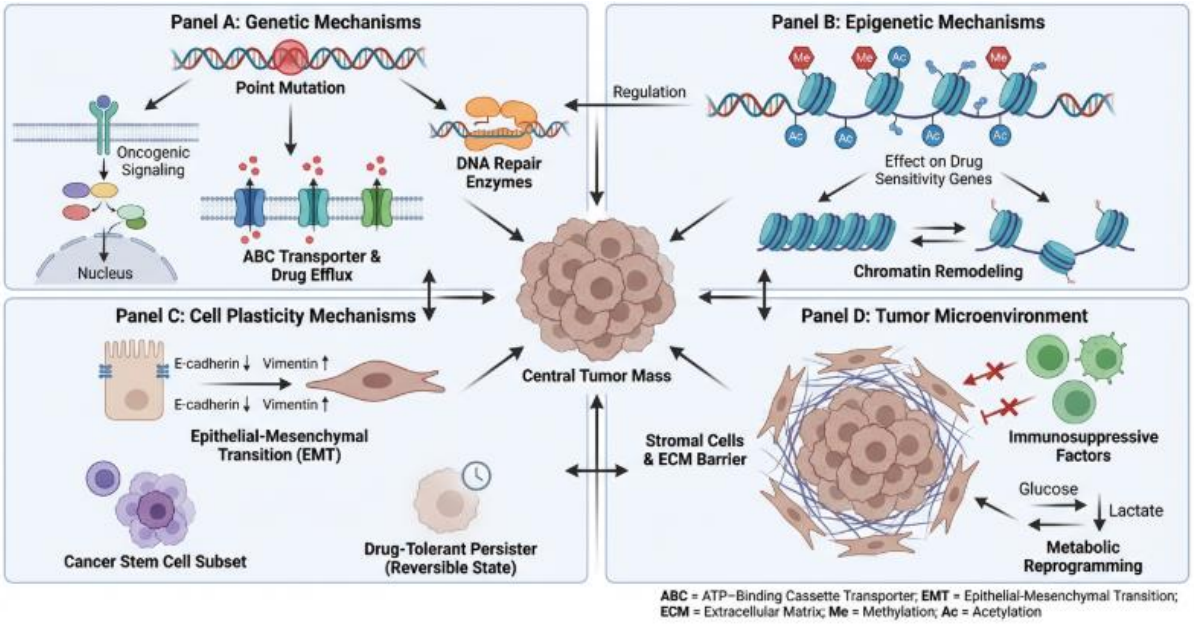

Figure 1: Multilevel mechanisms of cancer drug resistance.[5,14]

Caption: Multilevel mechanisms of cancer drug resistance. (A) Genetic mechanisms include target mutations, alterations in oncogenic pathways, overexpression of ABC transporters, and enhanced DNA repair. (B) Epigenetic mechanisms, including DNA methylation, histone modifications, and chromatin remodelling, affect the expression of drug-sensitivity genes. (C) Cell plasticity mechanisms, including EMT, cancer stem cell characteristics, and drug-tolerant persister states. (D) Tumour microenvironment contributions, including stromal barriers, immunosuppression, and metabolic reprogramming. The figure illustrates the interconnected nature of these mechanisms, with designated arrows showing crosstalk between pathways.

The emergence of resistance mutations follows predictable patterns based on structural constraints of the target protein. Gatekeeper mutations typically involve residues at the hinge region of kinase domains, where bulkier amino acids prevent inhibitor access while preserving ATP binding. Complementary resistance mechanisms include activation loop mutations and mutations affecting inhibitor-induced conformational changes.[9] Table 1 shows the Major Genetic Mechanisms of Drug Resistance in Cancer.

Table 1: Major Genetic Mechanisms of Drug Resistance in Cancer.

Mechanism	Examples	Clinical Impact	Key References
Target Mutations	EGFR T790M (NSCLC) ABL T315I (CML) BRAF V600E mutations	Reduces drug binding affinity; maintains kinase activity despite inhibitor presence	[8, 12]
Oncogenic Bypass Signaling	MET amplification PIK3CA mutations PTEN loss	Activates alternative pathways bypassing the inhibited target	[10, 11, 12]
Drug Target Amplification	HER2 amplification EGFR amplification BCR-ABL amplification	Increases target protein levels,overwhelming inhibitor capacity	[13]
ABC Transporter Overexpression	P-glycoprotein (ABCB1) MRP1 (ABCC1) BCRP (ABCG2)	Reduces intracellular drug concentration through active efflux	[14, 15, 16, 17, 18]
Enhanced DNA Repair	ERCC1 upregulation BRCA reversion mutations PARP1 mutations	Increases capacity to repair chemotherapy-induced DNA damage	[21, 22, 23, 24, 25, 26]

Oncogenic Pathway Alterations

Cancer cells can circumvent targeted therapy through activation of alternative signalling pathways that bypass the inhibited target. This bypass mechanism maintains proliferative and survival signals despite effective target inhibition.[10,11] MET amplification occurs in 5-20% of EGFR-mutant NSCLC patients treated with EGFR TKIs, providing an alternative receptor tyrosine kinase signal that activates downstream PI3K/AKT and MAPK pathways independent of EGFR.[12] Similarly, PIK3CA mutations or PTEN loss activate PI3K/AKT signalling, conferring resistance to HER2-targeted therapies in breast cancer.

Oncogene amplification represents another critical genetic mechanism. Amplification of the drug target itself can overwhelm inhibitor capacity, requiring higher drug concentrations for effective inhibition. HER2 amplification levels correlate with trastuzumab sensitivity in breast cancer, with highly amplified tumours showing better responses but also greater capacity for resistance through further amplification.[13]

Drug Efflux Transporters

ATP-binding cassette (ABC) transporters constitute a superfamily of membrane proteins that actively efflux cytotoxic compounds, reducing intracellular drug concentrations below therapeutic thresholds.[14,15] Three ABC transporters play predominant roles in multidrug resistance (MDR): P-glycoprotein (ABCB1/P-gp), multidrug resistance-associated proteins (ABCC/MRPs), and breast cancer resistance protein (ABCG2/BCRP). Figure 2 illustrates the ABC transporter-mediated multidrug resistance.

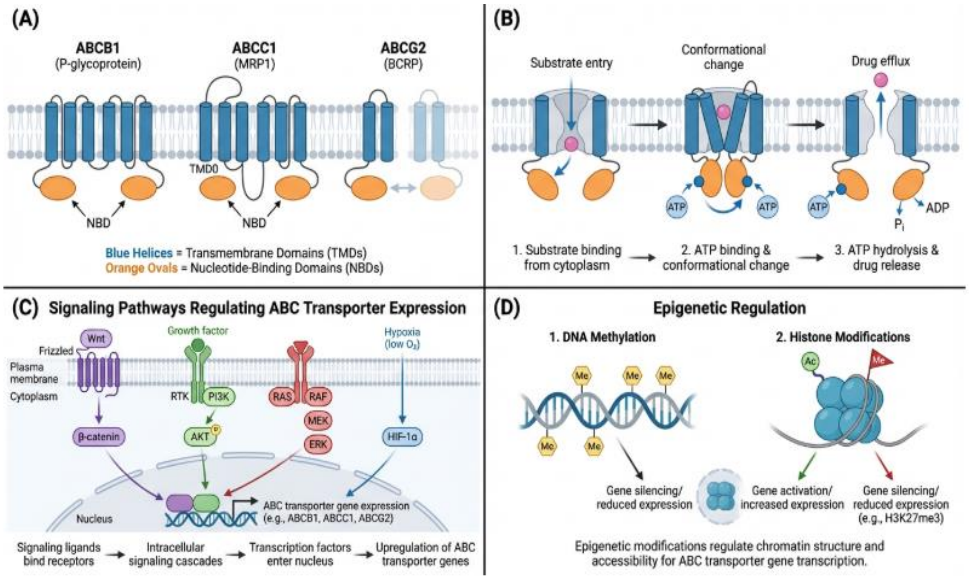

Figure 2: ABC transporter-mediated multidrug resistance.[14,16,17,19,20]

Caption: ABC transporter-mediated multidrug resistance. (A) Structural organisation of P-glycoprotein (ABCB1), MRP1 (ABCC1), and BCRP (ABCG2) showing transmembrane domains and nucleotide-binding

domains. (B) Mechanism of ATP-dependent drug efflux showing substrate entry, ATP hydrolysis, and conformational changes leading to extracellular drug release. (C) Signalling pathways regulating ABC transporter expression, including Wnt/β-catenin, PI3K/AKT, MAPK, and HIF-1α pathways. (D) Epigenetic regulation through DNA methylation and histone modifications.

P-glycoprotein functions as a broad-spectrum efflux pump, recognising structurally diverse chemotherapeutic agents including anthracyclines, taxanes, vinca alkaloids, and epipodophyllotoxins.[16] Overexpression results from gene amplification, increased transcription, or epigenetic modifications affecting ABCB1 promoter activity. ABCC1/MRP1 preferentially transports drug-glutathione, drug-glucuronide, and drug-sulphate conjugates, effectively exporting both native drugs and their metabolites.[17] ABCG2/BCRP, a half-transporter requiring homodimerization for function, confers resistance to mitoxantrone, topotecan, methotrexate, and several tyrosine kinase inhibitors.[18]

Transcriptional regulation of ABC transporters involves multiple pathways, including Wnt/β-catenin, PI3K/AKT, MAPK, and hypoxia-inducible factor-1α (HIF-1α), connecting drug resistance to a broader oncogenic signalling network.[19] Epigenetic modifications, particularly DNA methylation and histone acetylation, further modulate ABC transporter expression, providing reversible mechanisms for resistance acquisition.[20]

DNA Repair Mechanisms

Enhanced DNA repair capacity enables cancer cells to efficiently repair chemotherapy-induced DNA damage, reducing therapeutic efficacy.[21,22] Multiple DNA repair pathways contribute to resistance.

Base excision repair (BER) removes small base lesions caused by alkylating agents and oxidative stress. Upregulation of BER components, particularly DNA polymerase β and XRCC1, correlates with resistance to temozolomide and platinum compounds.[23] Nucleotide excision repair (NER) removes bulky DNA adducts formed by platinum-based chemotherapy. Enhanced NER activity, driven by increased expression of ERCC1, XPD, and XPA, significantly reduces platinum sensitivity in ovarian and lung cancers.[24]

Homologous recombination (HR) and non-homologous end joining (NHEJ) repair DNA double-strand breaks induced by topoisomerase inhibitors and ionising radiation. BRCA1/2 mutations impair HR, creating synthetic lethality with PARP inhibitors in ovarian and breast cancers.[25] However, reversion mutations restoring BRCA1/2 function represent a major resistance mechanism to PARP inhibitors, highlighting the dynamic nature of DNA repair-mediated resistance.[26] Figure 3 shows the DNA repair pathways and therapeutic resistance.

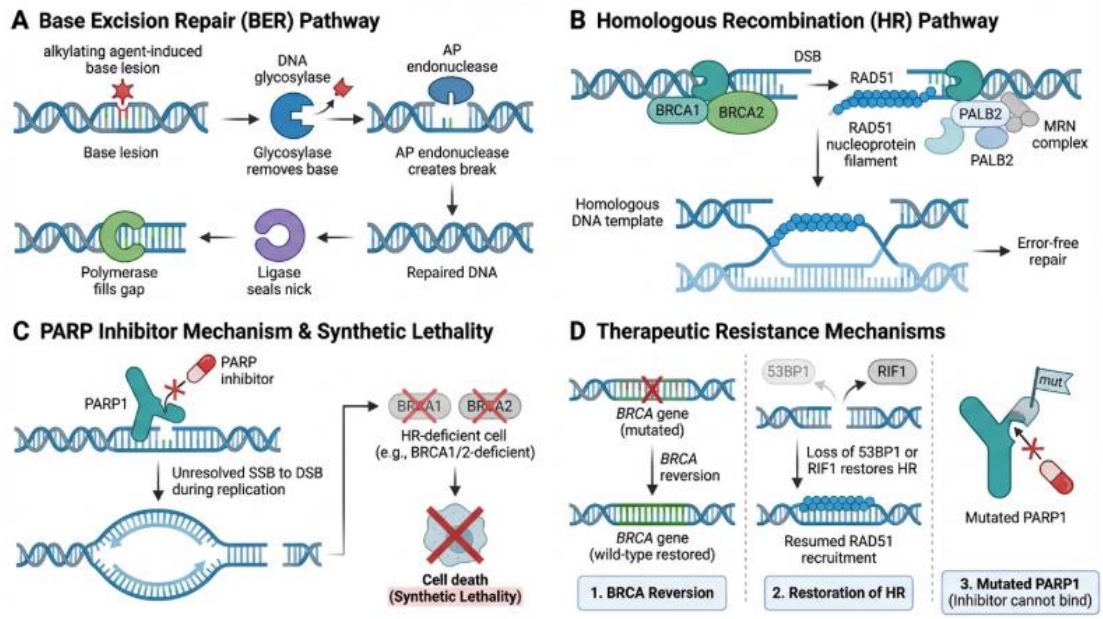

Figure 3: DNA repair pathways and therapeutic resistance.[21,25,26]

Caption: DNA repair pathways and therapeutic resistance. (A) Base excision repair (BER) pathway components are involved in repairing alkylating agent-induced damage. (B) Homologous recombination pathway showing BRCA1/2, RAD51, and associated proteins involved in double-strand break repair. (C) PARP inhibitor mechanism and synthetic lethality in HR-deficient cancers. (D) Resistance mechanisms include BRCA reversion mutations, restoration of HR through loss of 53BP1/RIF1, and PARP1 mutations affecting drug binding.

Epigenetic Mechanisms of Drug Resistance

DNA Methylation

Aberrant DNA methylation patterns profoundly influence drug sensitivity through transcriptional silencing of tumour suppressor genes and activation of oncogenes.[27,28] Hypermethylation of CpG islands in gene promoter regions causes transcriptional repression through recruitment of methyl-CpG-binding proteins and histone deacetylases, establishing repressive chromatin states.

Methylation-mediated silencing of apoptotic genes, including DAPK, TMS1, and caspase-8, enables cancer cells to evade chemotherapy-induced apoptosis.[29] Conversely, global DNA hypomethylation activates normally silenced repetitive elements and promotes chromosomal instability, contributing to tumour evolution and resistance development.[30] MGMT promoter methylation paradoxically predicts a favourable response to alkylating agents in glioblastoma by preventing DNA repair, whereas MGMT expression confers resistance.[31]

DNA methyltransferases (DNMTs) - DNMT1, DNMT3A, and DNMT3B - establish and maintain methylation patterns, while TET enzymes catalyse DNA demethylation through 5-methylcytosine oxidation.[32] Dysregulation of these enzymes alters the cancer methylome, influencing drug resistance phenotypes. Clinical application of DNMT inhibitors (azacitidine, decitabine) demonstrates that epigenetic modifications represent reversible, druggable resistance mechanisms.[33]

Histone Modifications

Post-translational histone modifications, including acetylation, methylation, phosphorylation, and ubiquitination, regulate chromatin structure and gene expression without altering DNA sequence.[34,35] Histone acetylation generally promotes transcriptional activation by relaxing chromatin, while deacetylation compacts chromatin and represses transcription. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) dynamically regulate acetylation status, with HDAC overexpression commonly observed in resistant cancers.[36]

Histone methylation shows complex, site-specific effects on transcription. H3K4me3 and H3K36me3 marks associate with active transcription, while H3K9me3 and H3K27me3 correlate with gene silencing.[37] Polycomb repressive complex 2 (PRC2), containing the H3K27 methyltransferase EZH2, frequently shows aberrant activity in resistant cancers, silencing tumour suppressors and differentiation genes while promoting stem cell characteristics.[38]

Histone modifications influence drug resistance through multiple mechanisms: altering expression of drug metabolism genes, modulating DNA repair capacity, regulating apoptotic machinery, and controlling epithelial-mesenchymal transition (EMT) programs.[39,40] HDAC inhibitors demonstrate clinical activity in hematologic malignancies and show promise in combination with chemotherapy for reversing resistance in solid tumours.[41] Table 2 shows the Epigenetic Modifications Contributing to Drug Resistance.

Table 2: Epigenetic Modifications Contributing to Drug Resistance.

Modification Type	Mechanism	Effect on Drug Resistance	Therapeutic Target	References
DA Hypermethylation	CpG island methylation in promoter regions	Silences tumour suppressors and pro-apoptotic genes (DAPK, TMS1, caspase-8)	DNMT inhibitors (azacitidine, decitabine)	[27, 28, 29]
DNA Hypomethylation	Global demethylation of repetitive elements	Promotes chromosomal instability and tumour evolution	TET enzyme modulators	[30, 32]
MGMT Methylation	Promoter methylation silencing MGMT expression	Paradoxically increases sensitivity to alkylating agents in glioblastoma	Biomarker for treatment selection	[31]
Histone Acetylation	HAT/HDAC dysregulation	Alters chromatin accessibility; regulates drug metabolism, DNA repair, and apoptosis genes	HDAC inhibitors (vorinostat, romidepsin)	[34, 35, 36,]
Histone Methylation	H3K27me3 by EZH2/PRC2 H3K4me3 alterations	Silences tumour suppressors; promotes stem cell characteristics	EZH2 inhibitors (tazemetostat)	[37, 38]
Chromatin Remodeling	SWI/SNF complex mutations (ARID1A, BRG1) CHD4 overexpression	Alters DNA damage response and drug sensitivity	Synthetic lethality approaches with PARP/ATR inhibitors	[42, 43, 44]

Chromatin Remodeling

ATP-dependent chromatin remodelling complexes - including SWI/SNF, ISWI, CHD, and INO80 families - regulate nucleosome positioning and chromatin accessibility, controlling gene expression programs relevant to drug sensitivity.[42] SWI/SNF complex

components are frequently mutated in cancer, with ARID1A mutations occurring in 10-20% of diverse tumour types.[42] These mutations alter chromatin landscapes, affecting sensitivity to PARP inhibitors, platinum agents, and immunotherapy.

BRG1 and BRM, the catalytic ATPase subunits of SWI/SNF complexes, show opposing roles in different contexts. BRG1 loss correlates with resistance to topoisomerase inhibitors but increased sensitivity to PARP inhibitors, reflecting synthetic lethal interactions between chromatin remodelling and DNA repair pathways.[42,43] CHD4, a component of the NuRD complex, regulates DNA damage response and confers resistance to genotoxic chemotherapy when overexpressed.[44]

Table 3: Clinical Trials Targeting Drug Resistance Mechanisms (2023-2025).

Strategy	Agent(s)	Cancer Type	Mechanism Targeted	References
Epigenetic Modulation + Chemotherapy	DNMT inhibitors + venetoclax	Acute myeloid leukemia	Reverses methylation-mediated resistance	[33, 71]
DNA Repair Inhibition + Targeted Therapy	PARP inhibitor (talazoparib) + enzalutamide	Metastatic prostate cancer	Exploits HR deficiency; prevents PARP-mediated DNA repair	[25, 72, 73]
DNA-PKcs/mTOR Inhibition	CC-115	Glioblastoma	Dual inhibition of DNA repair and proliferation pathways	[74]
Immunotherapy + Radiotherapy	Anti-PD-1/PD-L1 + radiation	Multiple solid tumours	Overcomes immune evasion; enhances tumour antigen presentation	[11, 75]
ABC Transporter Modulation	Nanoparticle delivery systems	Colorectal cancer, CNS tumours	Bypasses P-gp/BCRP-mediated efflux	[15, 19, 74]
TME Remodeling	CAF-targeted therapies + chemotherapy	Pancreatic, breast cancer	Improves drug delivery; reduces stromal barriers	[75, 76]

Cell Plasticity and Phenotypic Resistance

Epithelial-Mesenchymal Transition

EMT represents a developmental program reactivated in cancer, enabling epithelial cells to acquire mesenchymal characteristics, including enhanced motility, invasiveness, and therapeutic resistance.[46,47] EMT is orchestrated by transcription factors including SNAIL, SLUG, TWIST, and ZEB1/2, which repress epithelial markers (E-cadherin, claudins) while inducing mesenchymal markers (N-cadherin, vimentin, fibronectin).

EMT-mediated resistance operates through multiple mechanisms: upregulation of ABC transporters, enhanced DNA repair capacity, activation of survival pathways (PI3K/AKT, MAPK), and acquisition of stem cell properties.[46,47] Importantly, EMT represents a spectrum of transitional states rather than a binary switch, with partial EMT (hybrid E/M phenotype) showing particular association with aggressive behaviour and therapy resistance.[45,48]

TGF-β signalling represents a major EMT inducer, activating SMAD-dependent transcription of EMT transcription factors.[49] Tumour microenvironment factors, including hypoxia, inflammatory cytokines, and cancer-associated fibroblast secretions, further promote EMT, connecting cell-intrinsic resistance mechanisms to extrinsic microenvironmental influences.[50]

Cancer Stem Cells

Cancer stem cells (CSCs) represent a subpopulation with stem-like properties, including self-renewal capacity, tumour-initiating ability, and intrinsic therapy resistance.[52,53] CSCs exhibit multiple resistance mechanisms: quiescence (reduced cycling minimises sensitivity to cycle-dependent chemotherapy), enhanced ABC transporter expression, elevated aldehyde dehydrogenase activity (drug detoxification), robust DNA repair, and apoptosis resistance.[52,53]

CSC characteristics are maintained by stem cell pathways including Wnt/β-catenin, Hedgehog, Notch, and Hippo/YAP.[51,54] These pathways regulate self-renewal genes (OCT4, SOX2, NANOG) and differentiation programs. Importantly, CSC states show plasticity, with non-CSCs capable of dedifferentiating into CSCs under therapeutic pressure or microenvironmental cues.[55] This plasticity challenges the hierarchical CSC model and suggests that CSC-targeted therapies must account for dynamic state transitions.

Evidence from lineage tracing studies demonstrates that targeted therapy eliminates differentiated cancer cells while sparing CSC populations, which subsequently repopulate tumours with resistant phenotypes.[56] CSC enrichment following chemotherapy has been documented across multiple cancer types, with increased expression of CSC markers (CD44, CD133, ALDH1) correlating with poor outcomes.[57]

Non-Genetic Resistance Mechanisms

Recent evidence reveals that drug resistance can emerge without genetic mutations, through reversible epigenetic and transcriptional changes that enable rapid adaptation

to therapeutic stress.[5,6] Single-cell analyses demonstrate that isogenic cancer cell populations exhibit substantial phenotypic heterogeneity, with drug-tolerant persister cells pre-existing within tumours before treatment.[58]

Drug-tolerant persisters enter slow-cycling states characterised by distinct chromatin landscapes, activated stress response pathways, and metabolic reprogramming.[58,59] These cells can survive initial therapy, eventually proliferating to cause relapse. Importantly, persister states are reversible, with cells reverting to drug-sensitive phenotypes upon drug withdrawal, but capable of rapidly re-entering tolerance upon re-treatment.[59,60]

Transcriptional plasticity enables cancer cells to access alternative transcriptional programs that support survival under drug treatment. Melanoma cells treated with BRAF inhibitors activate receptor tyrosine kinases and reprogram metabolic pathways through transcription factor networks independent of genetic changes.[61] These adaptive transcriptional rewiring provides time for acquisition of permanent genetic alterations, serving as a bridge to stable resistance.

Tumour Microenvironment Contributions

The tumour microenvironment (TME) encompasses cellular (cancer-associated fibroblasts, immune cells, endothelial cells) and non-cellular (extracellular matrix, cytokines, chemokines) components that collectively influence therapeutic responses.[62,63,64] TME-mediated resistance operates through multiple mechanisms.

Physical barriers: Dense extracellular matrix and elevated interstitial pressure impede drug penetration, particularly affecting large molecules like antibodies.[64,65] Cancer-associated fibroblasts secrete collagen, fibronectin, and hyaluronic acid, creating fibrotic barriers that reduce chemotherapy delivery to tumour cells.[50]

Immunosuppression: Tumour-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells create immunosuppressive environments that inhibit anti-tumour immunity and reduce efficacy of immunotherapies.[66,67] TAMs secrete growth factors and cytokines (TGF-β, IL-10, VEGF) that promote tumour survival and angiogenesis while suppressing cytotoxic T cells.[66]

Metabolic reprogramming: TME hypoxia activates HIF-1α, inducing glycolytic metabolism, angiogenesis, and expression of ABC transporters.[68] Competition for nutrients (glucose, glutamine) and accumulation of metabolic waste products (lactate) further stress both cancer and immune cells, generally favouring cancer cell survival.[69]

Therapeutic Implications and Future Directions

Understanding resistance mechanisms enbles rational design of combination therapies targeting multiple resistance pathways simultaneously.[70] Several strategies show promise.

Targeting epigenetic regulators: Combining DNMT inhibitors, HDAC inhibitors, or EZH2 inhibitors with conventional chemotherapy re-sensitizes resistant cancers by reversing epigenetic silencing of tumour suppressors and pro-apoptotic genes.[33,71,72]

Inhibiting DNA repair: PARP inhibitors exploit synthetic lethality in HR-deficient cancers, while combinations of PARP, ATR, CHK1, or DNA-PKcs inhibitors create synergistic DNA damage in HR-proficient tumours.[73,74]

Targeting ABC transporters: Although direct ABC transporter inhibitors failed in clinical trials due to toxicity and drug interactions, alternative approaches including nanoparticle-based drug delivery and development of non-substrate chemotherapeutics show potential.[3,16]

Modulating tumour microenvironment: Strategies targeting cancer-associated fibroblasts, reprogramming TAMs, or normalizing tumour vasculature aim to enhance drug delivery and restore anti-tumour immunity.[74,75]

Preventing resistance emergence: Adaptive therapy, where treatment is modulated based on tumour response to maintain a population of drug-sensitive cells that compete with resistant clones, represents a paradigm shift from continuous maximum tolerated dose approaches.[76]

CONCLUSION

Drug resistance in cancer arises through multilevel mechanisms spanning genetic mutations, epigenetic reprogramming, cellular plasticity, and tumour microenvironment remodelling. These mechanisms do not operate independently but rather form interconnected networks that collectively enable cancer cells to evade therapeutic pressure. Genetic alterations provide stable, heritable resistance, while epigenetic modifications and cell plasticity enable rapid, reversible adaptation to treatment stress. The tumour microenvironment further facilitates resistance through physical barriers, immunosuppression, and metabolic reprogramming.

Effective strategies to overcome resistance require combination approaches targeting multiple mechanisms simultaneously, along with adaptive treatment paradigms that account for tumour evolution. Continued advances in single-cell technologies, spatial transcriptomics, and functional genomics will further elucidate resistance mechanisms and identify new therapeutic vulnerabilities. Ultimately, understanding and targeting drug resistance mechanisms represents the key to improving outcomes for cancer patients.

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