

Decoding Tumor Drug Resistance: Present Status and Future Landscapes

Abstract

Tumor drug resistance remains a significant challenge in cancer therapy, leading to treatment failure and disease progression. Understanding the mechanisms underlying drug resistance is crucial for developing effective strategies to overcome it. This review discusses the recent advances in the mechanisms of tumor drug resistance, including genetic and epigenetic alterations, the role of the tumor microenvironment, and cancer stem cells. It also explores the latest approaches to circumvent drug resistance, such as targeted therapies, combination treatments, nanotechnology-based drug delivery systems, immunotherapies, and epigenetic therapies. The review highlights the clinical implications of these advances and outlines future directions for research to improve patient outcomes.

Keywords: Tumor drug resistance; cancer therapy; genetic mutations; epigenetics; tumor microenvironment; cancer stem cells; targeted therapy; immunotherapy; nanotechnology; combination therapy.

1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, despite significant advances in diagnosis and treatment (Bray et al., 2018). A major hurdle in effective cancer therapy is drug resistance, which leads to treatment failure and disease recurrence (Holohan et al., 2013). Drug resistance in cancer therapy is a complex process primarily driven by alterations in drug targets. Tumor cells can develop resistance to chemotherapy, targeted agents, and even novel immunotherapies through various mechanisms. Resistance to anticancer agents arises from various factors, including individual genetic differences, particularly in tumor somatic cells. Cancer drug resistance can also be acquired and occurs through diverse mechanisms, such as multidrug resistance, suppression of cell death (apoptosis inhibition), alterations in drug metabolism, epigenetic modifications, changes in drug targets, enhanced DNA repair capabilities, and gene amplification (Mansoori et al., 2017).

Understanding the complex biological processes that contribute to drug resistance is essential for developing strategies to overcome it. Advances in DNA microarray technology, proteomics, and the development of targeted therapies have introduced new strategies to address this challenge. However, despite the rapid progress in designing novel chemotherapeutic agents, an effective treatment for advanced stages of cancer, such as invasion and metastasis, remains elusive (Mansoori et al., 2017). Recent research has provided insights into genetic and epigenetic alterations, the role of the tumor microenvironment, and the presence of cancer stem cells in mediating resistance (Vasan et al., 2019). This review summarizes the current knowledge on tumor drug resistance mechanisms and discusses recent advances in overcoming resistance to improve therapeutic outcomes.

2. Mechanisms of Tumor Drug Resistance

2.1. Genetic Mechanisms

Genetic alterations play a significant role in the development of drug resistance. These changes can affect drug targets, signaling pathways, and cellular processes essential for drug efficacy.

2.1.1. Gene Mutations

Mutations in genes encoding drug targets can render therapies ineffective. Increasing evidence has shown that aberrant epigenetic regulations contribute to tumor resistance. Mutations in drug transporters impair their function, leading to reduced drug absorption. Resistance to methotrexate frequently arises due to mutations in the human folate carrier (hRFC) gene, particularly in patients with acute lymphoblastic leukemia (ALL). A specific mutation at nucleotide 133, where guanine (G) is altered, results in the substitution of lysine with glutamic acid in the first transmembrane domain of the hRFC protein. This change reduces the transporter's affinity for methotrexate, diminishing the drug's effectiveness (Mansoori et al., 2017). Mutations in the *EGFR* gene lead to resistance to tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) patients (Oxnard et al., 2011). The T790M mutation in *EGFR* decreases the binding affinity of first-generation TKIs, necessitating the development of third-generation inhibitors like osimertinib (Mok et al., 2017) (Wang et al., 2023). The drug resistance occurred by the mutations in the p53 gene, can induce apoptosis in the cell stress and DNA damaging. These mutations could impair the connection between DNA damage (which caused by chemotherapeutic agents) and the activation of apoptosis. Drug resistance driven by mutations in the p53 gene significantly impacts the cellular response to stress and DNA damage. The p53 protein plays a crucial role in inducing apoptosis in response to cellular stress and DNA damage caused by chemotherapeutic agents. Mutations in the p53 gene can disrupt this pathway, impairing the link between DNA damage and the activation of apoptosis. As a result, tumor cells with p53 mutations can evade apoptosis, contributing to resistance against chemotherapy and reducing the effectiveness of treatment (de Vree et al., 1998). One of the most prevalent forms of drug resistance, driven by secondary mutations and alterations in drug targets, is imatinib resistance in chronic myelogenous leukemia (CML). In CML, the formation of the Philadelphia chromosome—a hallmark genetic abnormality—results from a translocation between chromosomes 9 and 22. This translocation joins the 3' end of the *ABL* gene on chromosome 9 with the 5' end of the *BCR* gene on chromosome 22, creating the *BCR-ABL* fusion gene. This fusion gene encodes a constitutively active tyrosine kinase, which is the primary target of imatinib. However, secondary mutations within the *BCR-ABL* kinase domain can alter the drug-binding site, rendering imatinib less effective and leading to resistance (Holohan et al., 2013).

2.1.2. Gene Amplification

Gene amplification is a significant mechanism of drug resistance observed in approximately 10% of cancers, particularly in leukemias. Amplification of genes can result in overexpression of proteins that promote cell survival and proliferation, contributing to drug resistance. This resistance occurs as cancer cells increase the number of copies of the Dihydrofolate reductase (DHFR) gene, which encodes the target enzyme for methotrexate. Gene amplification can elevate the number of oncogene copies in a single cell by several hundred-fold, leading to the production of excessive amounts of the associated oncoproteins. In cancer cells, these amplified sequences can be identified by the presence of additional

small chromosomes (Mansoori et al., 2017). The MET proto-oncogene (hereafter referred to as MET) encodes a receptor tyrosine kinase known as the hepatocyte growth factor (HGF) receptor. Together with its ligand HGF—forming the HGF/MET axis—it serves as an essential regulator of cell survival, proliferation, motility, and migration. Dysregulation of MET signaling has been observed in various cancers through multiple mechanisms, such as activating point mutations in the MET gene, overexpression of the ligand HGF, copy number gain or amplification of the MET gene (MET-CNG), and MET gene fusions. MET amplification occurs in 1–6% of Non-small cell lung cancer (NSCLC) cases and was considered as a negative prognostic factor (Qin et al., 2023). The amplification of the *MET* gene leads to resistance in EGFR-mutant NSCLC by activating alternative signaling pathways (Engelman et al., 2007), (Liam et al., 2023) (Li et al., 2024)

2.2. Epigenetic Mechanisms

Epigenetic alterations, such as DNA methylation, histone modifications, and non-coding RNA expression, can regulate gene expression without changing the DNA sequence. These changes can lead to the silencing of tumor suppressor genes or activation of oncogenes, contributing to drug resistance (Sharma et al., 2010). Epigenetic modifiers—including microRNAs (miRNAs), histone methyltransferases (HMTs)/demethylases, and DNA methyltransferases/demethylases—are associated with cancer proliferation, metastasis, angiogenesis, and drug resistance. DNA methylation is a key epigenetic process involving the addition of a methyl group to cytosine residues, catalyzed by DNA methyltransferases. While methylation predominantly occurs at cytosine sites, it can also occur at other genomic regions. Similarly, acetylation and deacetylation of specific lysine residues at the terminal ends of histones and non-histone proteins are regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively. These enzymatic modifications influence the structure and composition of chromatin, affecting gene expression (Mansoori et al., 2017). HMTs are frequently overexpressed in various cancers, and recent studies have increasingly identified these proteins as potential therapeutic targets (Han et al., 2024). Hypermethylation of the *MLH1* gene promoter results in reduced DNA mismatch repair capacity and resistance to alkylating agents (Zhu et al., 2023).

2.3. Drug Efflux Pumps

Overexpression of drug efflux transporters, such as P-glycoprotein (P-gp) encoded by the *ABCB1* gene, leads to decreased intracellular drug accumulation and reduced efficacy (Robey et al., 2018). Cancer cells can upregulate these pumps in response to chemotherapy, contributing to multidrug resistance. The overexpression of P-glycoprotein (P-gp) in cancer cells is influenced by several factors, including adenosine triphosphate (ATP) hydrolysis, hypoxia-inducible factor 1 alpha (HIF-1 α), and the physicochemical properties of drugs such as lipophilicity, molecular weight, and molecular size. Additionally, repeated exposure to anticancer drugs interacting with the P-gp efflux protein can lead to an acquired overexpression of P-gp (Halder et al., 2022).

2.4. DNA Repair Mechanisms

Enhanced DNA repair capacity allows tumor cells to survive DNA-damaging agents. Chemotherapeutic agents exert their effects by directly or indirectly damaging the DNA of cancer cells. However, cancer cells have mechanisms to repair this damage, which can contribute to drug resistance. Epigenetic mechanisms can also impact DNA repair systems. In

the mismatch repair (MMR) system, several proteins, including hMLH1 and hMSH1, play crucial roles. Mutations or hypermethylation of promoters in these genes can disrupt DNA repair, leading to cancer. For instance, hypermethylation or mutation of the hMLH1 gene promoter is closely associated with the development of colorectal cancer (Smith et al., 2015). Platinum-based agents like cisplatin induces DNA damage, ultimately triggering apoptosis in tumor cells. Resistance to drugs often arises through enhanced DNA repair mechanisms, such as the nucleotide excision repair (NER) system and homologous recombination repair (HRR) pathways, which restore DNA integrity and reduce the effectiveness of the therapy (Mansoori et al., 2017). Overexpression of DNA repair proteins like ERCC1 leads to resistance to platinum-based chemotherapy (Galluzzi et al., 2012). Similarly, mutations in BRCA1/2 genes affect homologous recombination repair, influencing sensitivity to PARP inhibitors (Lord & Ashworth, 2016).

2.5. Tumor Microenvironment

The tumor microenvironment (TME) plays a critical role in drug resistance. There are many evidences that prove the critical role of the tumor microenvironment (TME) in driving drug resistance, which remains a major cause of cancer relapse and treatment failure. The TME comprises normal stromal cells, the extracellular matrix (ECM), and soluble factors such as cytokines and growth factors. Tumor-tumor cell communication, tumor-stromal cell communication, as well as tumor-ECM interface, all contribute to direct cell interaction mediated by drug resistance. Additionally, soluble factors secreted within the TME provide signals that promote tumor cell growth and survival. Environment-mediated drug resistance (EM-DR) encompasses two main mechanisms: cell adhesion-mediated drug resistance (CAM-DR) and soluble factor-mediated drug resistance (SM-DR), both arising from complex tumor-host interactions (Li and Dalton, 2006). Components such as cancer-associated fibroblasts (CAFs), immune cells, and extracellular matrix (ECM) contribute to a protective niche for tumor cells (Meads et al., 2009). Hypoxia within the TME can induce hypoxia-inducible factors (HIFs), leading to altered gene expression and resistance to therapies (Vaupel & Mayer, 2016).

2.6. Cancer Stem Cells

Cancer stem cells (CSCs) possess self-renewal capabilities and contribute to tumor heterogeneity. Cancer stem-cell populations have been detected in a variety of hematopoietic and solid tumors, and might be the cell of origin of hematopoietic and solid tumors. Although chemotherapy impairs an enormous number of cells in a tumor, but it is understood that the chemotherapy agents are removed from cancer stem cells with the special mechanisms, which might be an important for drug resistance, for instance, overexpression of the ATP-binding cassette (ABC), drug transporters such as ABCB1, which encodes P-glycoprotein, and the ABCG2, which was originally identified in mitoxantrone resistant cells have been shown to keep cancer stem cells away from chemotherapeutic agents. Cancer stem cells share several of normal stem cells possession that provides for a long lifetime, including the relative silence, resistance to drugs and toxins through the expression of drug efflux transporters, an active DNA-repair capacity and a resistance to apoptosis, vascular niche, dormancy, hypoxic stability and enhance activity of repair enzymes. Targeting CSCs is crucial for preventing relapse and metastasis. (Dean et al., 2005), (Pal et al., 2016), (Mansoori et al., 2017) (Phi et al., 2018).

3. Advances in Overcoming Drug Resistance

Multidrug resistance (MDR) in cancer cells, whether intrinsic or acquired through various mechanisms, poses a significant challenge to the therapeutic efficacy of anticancer drugs. One of the primary reasons for reduced drug performance is the overexpression of ATP-binding cassette (ABC) transporter proteins on the cell membrane. These transporters limit drug uptake, enhance drug detoxification, and facilitate efficient DNA repair, thereby contributing to resistance. Additionally, MDR cancer phenotypes are characterized by physiological abnormalities, increased blood flow, an elevated apoptotic threshold, and enhanced drug efflux capabilities. These challenges have prompted researchers to develop advanced therapeutic strategies to combat MDR. Key approaches include the co-delivery of drugs with different generations of MDR inhibitors, optimizing dosage regimens and frequency of drug administration, and employing combinatorial treatment options, altered therapeutic regimens, utilization of non-substrates, nanotechnology-based supramolecular designs, etc. These strategies aim to overcome resistance mechanisms, enhance drug efficacy, and improve clinical outcomes in cancer therapy (Duan et al., 2023).

3.1. Targeted Therapies

Targeted therapies aim to inhibit specific molecules involved in tumor growth and survival. The development of second- and third-generation inhibitors has addressed resistance due to mutations. Osimertinib, a third-generation EGFR-TKI, effectively overcomes T790M-mediated resistance in NSCLC (Soria et al., 2018). Similarly, ALK inhibitors like alectinib and ceritinib have been developed to target resistant ALK-rearranged tumors (Peters et al., 2017).

3.2. Combination Therapies

Combining therapies can enhance efficacy and prevent resistance by targeting multiple pathways. Combining BRAF inhibitors with MEK inhibitors in melanoma has improved outcomes and reduced resistance compared to monotherapy (Long et al., 2017). Combining chemotherapy with targeted agents or immunotherapies is also being explored to overcome resistance mechanisms.

3.3. Nanotechnology in Drug Delivery

With the advent of nanotechnology, significant advancements have enabled the development of innovative nano-sized constructs ranging from 1 to 100 nm. These nanometric designs exhibit superior physicochemical and morphological properties compared to their bulk counterparts with the same composition. Notably, their increased surface area and abundance of surface-active groups create extensive opportunities for functionalization. These features allow for the efficient encapsulation of therapeutic agents and the immobilization of targeting ligands, thereby enhancing the precision and efficacy of therapeutic delivery (Kankala et al., 2020). Nanoparticle-based drug delivery systems enhance drug accumulation in tumors and reduce systemic toxicity. Nanocarriers can bypass efflux pumps and deliver drugs directly to cancer cells (Torchilin, 2014). Various organic-based supramolecular designs have been proposed to address these shortcomings, such as polymers, liposomes, and dendrimers (Ray et al., 2018). Liposomal doxorubicin and nanoparticle albumin-bound paclitaxel are examples of nanotechnology applications improving drug efficacy (Bobo et al., 2016).

3.4. Immunotherapy Approaches

Immunotherapies, such as immune checkpoint inhibitors, have revolutionized cancer treatment by enhancing the immune system's ability to target tumors (Topalian et al., 2015). Overcoming resistance involves combination strategies and identifying biomarkers to predict response. CAR T-cell therapy is also being explored to target resistant tumors (June et al., 2018).

3.5. Epigenetic Therapies

Epigenetic drugs, like DNA methyltransferase inhibitors (e.g., azacitidine) and histone deacetylase inhibitors (e.g., vorinostat), can reverse epigenetic alterations contributing to drug resistance (Biswas & Rao, 2018). Combining epigenetic therapies with other treatments may enhance efficacy and overcome resistance.

3.6. Altered chemotherapy regimens

The primary objective of chemotherapy is to inhibit tumor cell proliferation, reduce tumor mass, and prevent invasion and metastasis. However, monotherapy, relying on a single drug, often leads to the development of resistance by tumor cells, rendering treatment less effective over time. To address this challenge, altered therapeutic regimens have emerged as a predominant strategy (Duan et al., 2023). These regimens typically involve the combination of two or more drugs administered at modified dosages, leveraging their synergistic effects to enhance efficacy. This approach not only reduces the likelihood of resistance by targeting multiple pathways simultaneously but also potentially minimizes toxicity by optimizing drug concentrations. Combination regimens have become a cornerstone in modern cancer treatment, improving outcomes for patients with resistant or advanced tumors. Similar to the reduction in toxicities, drug combinations significantly lower the likelihood of drug resistance development by targeting cancer cells through multiple mechanisms (Peters et al., 2000). This multi-targeted therapeutic approach, as exemplified by the combination of cisplatin and etoposide in the treatment of small cell lung cancer, enhances treatment efficacy. Additionally, combining drugs in later therapeutic regimens prevents the emergence of resistant clones by effectively eliminating highly proliferative and metastatic cells (Duan et al., 2023). This strategy disrupts adaptive resistance mechanisms, ensuring a more comprehensive eradication of tumor populations and reducing the potential for relapse. Several drug combinations, selecting one agent from each class, have been effectively utilized in cancer treatment. For example, the combination of Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD regimen) is commonly used for Hodgkin's lymphoma (Batty et al., 2012). Similarly (BEP regimen), a chemotherapy combination, used to treat ovarian and testicular germ cell tumors. It includes the drugs bleomycin sulfate, etoposide phosphate, and cisplatin (Platinol) (Behnia et al., 2000). These multi-class combinations leverage the unique mechanisms of action of each drug, enhancing therapeutic efficacy while minimizing the likelihood of resistance development.

3.7. P-gp inhibitors

A promising strategy to overcome multidrug resistance (MDR) in cancer therapy involves blocking the activity of the most prevalent efflux pump, P-glycoprotein (P-gp), by using effective transport inhibitors. These inhibitors can interfere with P-gp function, reverse drug

resistance, and enhance the intracellular accumulation of chemotherapeutic agents (Binkhathlan and Lavasanifar, 2013) (Robey et al., 2018) (Duan et al., 2023).

3.7.1 Generations of P-gp Inhibitors:

- **First-generation inhibitors** such as verapamil, quinidine, and cyclosporine A were among the initial efforts to inhibit P-gp, but their clinical use was limited by off-target effects and suboptimal efficacy (Nobili et al., 2006).
- **Second-generation inhibitors** like dexverapamil and dexniguldipine were developed to improve specificity and potency, yet they also encountered challenges, including drug-drug interactions (Szakács et al., 2006).
- **Third-generation inhibitors**, including zosuquidar and elacridar, showed greater promise in targeting P-gp selectively and reversing drug resistance. However, many of these modulators failed to achieve widespread clinical success due to unpredictable pharmacokinetics and adverse effects (Nobili et al., 2006).

Recent research has shifted focus toward **fourth-generation inhibitors**, derived from naturally occurring compounds such as alkaloids and flavonoids. These natural products are being explored for their ability to inhibit ABC transporters like P-gp with fewer side effects and improved biocompatibility, offering a potential breakthrough in overcoming MDR in cancer treatment (Karthikeyan and Hoti, 2015) (Duan et al., 2023).

4. Clinical Implications and Future Directions

Understanding tumor drug resistance mechanisms has significant clinical implications. Personalized medicine approaches, including genomic profiling, can identify mutations and guide therapy selection (Meldrum et al., 2011). Biomarkers predicting resistance can inform treatment decisions and improve outcomes.

Future research focuses on:

- **Identifying Novel Targets:** Ongoing studies aim to discover new molecular targets involved in resistance.
- **Developing Resistance Predictors:** Biomarkers and imaging techniques to predict resistance before therapy initiation.
- **Enhancing Drug Delivery:** Advances in nanotechnology and targeted delivery systems to improve drug accumulation in tumors.
- **Combination Strategies:** Optimizing combinations of therapies to prevent or overcome resistance.
- **Overcoming TME-Mediated Resistance:** Targeting components of the TME to disrupt protective niches.

5. Conclusion

Tumor drug resistance remains a significant obstacle in cancer therapy. Advances in understanding the underlying mechanisms have led to the development of novel therapeutic strategies. Targeted therapies, combination treatments, nanotechnology, immunotherapies, and epigenetic drugs offer promising approaches to overcome resistance. Ongoing research

and personalized medicine approaches are essential to improve patient outcomes and combat drug-resistant tumors effectively.

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