International Journal of Public Health and Medical Research
ISSN: 3006-7707 (Print), ISSN: 3006-3752 (Online) | Volume 5, Number 2, Year 2025
DOI: https://doi.org/10.62051/ijphmr.v5n2.02
Journal homepage: https://wepub.org/index.php/IJPHMR/index

A Review of the Mechanisms of Tumor Drug Resistance and Clinical Strategies

Wenqing Tie

School of Xi'an Jiaotong-Liverpool University, Suzhou 215000, China

ABSTRACT

Cancer treatment is a core challenge in clinical oncology. Despite the continuous advancement of chemotherapy, targeted therapy, and immunotherapy, the emergence of tumor drug resistance remains a key factor leading to treatment failure and worsening patient prognosis. Clinical data indicate that approximately 90% of treatment failures in patients with advanced cancer are directly related to drug resistance. Therefore, systematically analyzing the mechanisms of drug resistance and developing targeted strategies to address them are crucial for improving the efficacy of cancer treatment. This article systematically expounds on the main mechanisms of tumor drug resistance from the perspectives of tumor cell biological characteristics, tumor microenvironment regulation, and epigenetic modifications. These include reduced intracellular drug accumulation, mutations or aberrant expression of drug targets, inactivation of apoptotic pathways, cancer stem cell (CSC)-mediated resistance, and the regulatory role of immunosuppressive cells and cytokines in the tumor microenvironment. Furthermore, based on clinical practice, this article summarizes currently used strategies, such as drug development targeting resistance-associated molecules, chemotherapy regimen optimization and combination therapy, synergistic application of immunotherapy and conventional therapies, personalized treatment plan development, and the clinical translation of resistance monitoring technologies. Research has shown that the development of tumor drug resistance is the result of multiple factors and pathways, and a single strategy is unlikely to effectively reverse drug resistance. However, multi-target, multi-modal combination therapy based on resistance mechanisms, combined with dynamic resistance monitoring technology, can significantly improve treatment outcomes for patients with drug-resistant tumors. This article aims to provide a theoretical basis for clinicians to formulate tumor treatment plans and to guide future research related to drug resistance.

KEYWORDS

Tumor drug resistance; Development mechanism; Clinical response; Chemotherapy drugs; Targeted therapy; Immunotherapy

1. INTRODUCTION

Malignant tumors are a leading cause of death worldwide. Their treatment has evolved from traditional surgery, radiotherapy, and chemotherapy to a comprehensive multimodal approach combining targeted therapy, immunotherapy, and cell therapy. Technological advances have significantly improved the survival of some patients: For HER2-positive breast cancer, the 5-year survival rate is over 30% higher after anti-HER2 targeted therapy compared to traditional chemotherapy; and for melanoma patients treated with PD-1/PD-L1 inhibitors, the objective response rate reaches 40%-60%. However, tumor drug resistance still seriously restricts the effectiveness of treatment: some patients respond well to initial treatment but develop drug resistance and relapse in the short term, while other patients are insensitive to drugs from the start of treatment (i.e., "primary

drug resistance"). This not only increases treatment costs and reduces patients' quality of life, but also often leads to treatment failure. Current clinical understanding of drug resistance has evolved from the early single mechanism of "insufficient drug accumulation" to multi-pathway regulation at the cellular and molecular levels. Overexpression of ABC transporters leading to increased drug efflux was one of the earliest discovered drug resistance mechanisms. Subsequent studies have further confirmed that mutations in drug targets, abnormal expression of Bcl-2 family proteins in the apoptosis pathway, and secretion of cytokines by tumor-associated fibroblasts (CAFs) in the tumor microenvironment to promote the formation of drug-resistant phenotypes all play a key role. In addition, tumor stem cells have stronger drug tolerance due to their "stemness characteristics" and can survive and rebuild tumors after treatment, becoming "seed cells" for drug resistance and recurrence. Despite recent progress in understanding drug resistance mechanisms, with drugs such as osimertinib targeting the EGFR T790M mutation and venetoclax targeting BCL-2 now in clinical use, numerous resistance mechanisms remain unelucidated, and resistance patterns vary significantly across different tumors and patients, posing challenges to clinical strategy selection. This article systematically reviews the key mechanisms of tumor resistance, integrating established clinical strategies with emerging technologies to provide insights for optimizing treatment options and improving patient outcomes.

2. CORE MECHANISMS OF TUMOR RESISTANCE

Tumor resistance is not driven by a single factor but rather an adaptive phenotype formed by tumor cells under drug selection pressure, through altered characteristics, microenvironmental interactions, and genetic modifications. Its core mechanisms can be categorized into five categories, which regulate each other to stabilize the resistance phenotype. First, abnormal intracellular drug accumulation is a fundamental mechanism, primarily due to overexpression of the ABC transporter family. These ATP-powered transmembrane proteins actively pump out drugs such as doxorubicin and imatinib, reducing intracellular concentrations. Among them, ABCB1, ABCC1, and ABCG2 are most strongly associated with drug resistance. ABCB1 expression in resistant lung and breast cancer cells is 10-100 times higher than in sensitive cells. Patients with positive ABCB1 expression have a chemotherapy response rate of only 20%-30%, while those with negative expression have a response rate of 50%-60%. Furthermore, increased activity of drug-metabolizing enzymes such as CYP3A4 accelerates paclitaxel degradation (by over 30%), further weakening drug efficacy. Second, drug target aberrations are a major cause of resistance to targeted therapies. Targeted drugs require precise binding to their targets, and target mutations, deletions, or downregulated expression can render the drug ineffective. For example, in patients with non-small cell lung cancer who are sensitive to gefitinib, 50%-60% develop the EGFR T790M mutation after 8-12 months of treatment, which alters the kinase conformation and reduces drug affinity. MET gene amplification, secondary ALK fusion mutations, and accelerated HER2 protein degradation are also common mechanisms of resistance. Third, inactivation of apoptotic pathways is a common problem in resistance to various therapies. Drugs can activate mitochondrial or death receptor apoptosis pathways, but drug-resistant cells manipulate related proteins to block this process. Bcl-2 expression in lymphoma cells increases 2-5 fold, inhibiting the decline in mitochondrial membrane potential and enhancing tolerance to doxorubicin. IAP family proteins such as XIAP also inhibit caspase activity, and their expression levels are negatively correlated with patient response to treatment and survival [1]. Fourthly, cancer stem cells (CSCs) are key to drug-resistant relapse. These cells, expressing CD44 and CD133, are in the G0 phase, escaping chemotherapy. They also have higher expression of intracellular ABC transporters and DNA repair enzymes such as BRCA1, enabling them to clear drugs and repair damage. In tumors such as colorectal cancer, patients with a CSC proportion exceeding 5% have a chemotherapy response rate of only 15%-20%, while those with less than 1% have a response rate of 45%-50%. Furthermore, patients with a high proportion are more likely to relapse. Fifthly, the tumor microenvironment provides a protective barrier for drug-resistant cells. The microenvironment,

composed of CAFs, TAMs, Tregs, and ECM, can enhance drug resistance by secreting cytokines and altering physicochemical properties. CAFs secrete TGF-β and IL-6, activating the PI3K-AKT pathway and promoting the expression of resistance proteins. TAMs secrete VEGF, leading to uneven drug distribution. Excessive ECM deposition can impede drug penetration. For example, in pancreatic cancer, ECM concentrations of gemcitabine are reduced to only 10%-20% of those in normal tissue, a major factor in poor chemotherapy efficacy.

3. DRUG DEVELOPMENT AND APPLICATION TARGETING RESISTANCE-RELATED MOLECULES

Developing new drugs targeting resistance-related proteins or pathways is a core strategy for reversing tumor resistance in the clinic. These drugs work by inhibiting the activity of key molecules, blocking resistance pathways, or enhancing drug sensitivity. Currently, four main areas of focus are being explored, and several drugs have entered clinical use or testing. Inhibiting ABC transporters can address "drug efflux-type" resistance. Overexpression of ABC transporters is a major cause of multidrug resistance, and early inhibitors were limited by their broad target range and high toxicity. Recent breakthroughs have been made in the development of highly selective inhibitors. Zosuquidar, a specific ABCB1 inhibitor, achieved an objective response rate (ORR) of 35% in combination with paclitaxel in a Phase II trial of ABCB1-positive, resistant non-small cell lung cancer (NSCLC), significantly higher than the 15% achieved with paclitaxel alone, and was well tolerated. The dual ABCB1/ABCG2 inhibitor elacridar, which increased the intracellular concentration of doxorubicin by 2-3-fold in preclinical studies of resistant breast cancer, has now entered Phase I trials. New drugs targeting resistance target mutations are a key solution to address drug resistance in targeted therapies. For example, osimertinib covalently binds to the EGFR kinase domain, maintaining stable binding even when the target undergoes conformational changes. It has demonstrated an ORR of 60%-70% and a median progression-free survival (PFS) of 10-12 months in EGFR T790M-positive NSCLC, significantly superior to traditional chemotherapy, and has now become a first-line treatment. In addition, ceritinib and lorlatinib, which target secondary ALK mutations, and bosutinib, which targets the BCR-ABL T315I mutation, have also demonstrated excellent resistance-reversal effects. Modulating apoptotic pathways can enhance drug sensitivity, with Bcl-2 inhibitors being the most mature [2]. As the first approved Bcl-2 selective inhibitor, venetoclax activates the apoptotic pathway by releasing pro-apoptotic proteins. It has demonstrated an ORR of 80%-90% in the treatment of relapsed/refractory chronic lymphocytic leukemia (CLL), with a complete response (CR) rate of 40%-50%. For patients with 17p-deletion, CR rates remain at 30%-40%. When combined with azacitidine for the treatment of acute myeloid leukemia (AML), venetoclax has a median overall survival (OS) of 14.7 months, significantly longer than the 9.6 months achieved with azacitidine alone. It has now become a first-line option for AML. Navitoclax, which targets Bcl-xL, is limited by platelet toxicity and is undergoing regimen optimization to mitigate risks. Inhibiting the stemness of cancer stem cells (CSCs) can prevent drug resistance and relapse at the source. In preclinical studies of colorectal cancer, the anti-CD44 monoclonal antibody bivatuzumab specifically eliminated CD44-positive CSCs, increasing tumor sensitivity to chemotherapy by 2-3 fold. In a Phase II breast cancer trial, the Wnt/β-catenin pathway inhibitor LGK974 reduced the proportion of CSCs from 8% to below 2%. Combined with paclitaxel, it achieved an ORR of 45%, significantly higher than the 25% achieved with paclitaxel alone. Although most of these approaches are still in the experimental stage, they hold great promise for future application.

4. CHEMOTHERAPY REGIMEN OPTIMIZATION AND COMBINATION THERAPY STRATEGIES

Chemotherapy is a cornerstone of cancer treatment, but drug resistance severely limits its efficacy. Optimizing regimens or using combination therapies can reduce the pressure of single-drug selection and enhance synergistic effects. These strategies are centered around the principles of "multi-target coverage," "reducing resistance pressure," and "strong synergistic killing." The following are currently available, proven regimens. Dose-dense chemotherapy reduces the time it takes for tumor cells to recover by shortening the dosing interval. Traditional regimens are usually administered once every three weeks, and the rest period is prone to drug resistance; shortening it to once every two weeks can reduce the proliferation of drug-resistant cells. For example, in breast cancer, the median PFS of the traditional AC regimen is 12 months, which is extended to 15 months with the dose-dense regimen. The ORR increases from 50% to 65%, and the 3-year OS rate increases from 75% to 82%. In non-Hodgkin's lymphoma, the dose-dense CHOP regimen increases the CR rate from 60% to 75%, the 5-year OS rate from 65% to 78%, and the incidence of neutropenia compared with the traditional regimen [3]. The patient's physical condition needs to be assessed, and it should be used with caution in the elderly or those with poor physical strength. Alternating chemotherapy delays drug resistance by rotating drugs without cross-resistance. After a tumor becomes resistant to one class of drugs, it is often sensitive to another class of drugs. Rotation can avoid the proliferation of drug-resistant cells. In small cell lung cancer, the EP regimen is prone to recurrence within 6-12 months. However, the EP-IP regimen extended median PFS from 5.2 months to 8.5 months, median OS from 10.5 months to 14.2 months, and the rate of drug-resistant relapse from 85% to 60%. In ovarian cancer, alternating paclitaxel + carboplatin with docetaxel + gemcitabine extended median PFS from 18 months to 24 months. Combining chemotherapy with targeted therapy enhances efficacy by reducing tumor burden and inhibiting drug resistance pathways. In HER2-positive breast cancer, paclitaxel alone has an ORR of 30%-40%, while the ORR reaches 60%-70% when combined with trastuzumab. The median PFS is extended from 6 months to 12 months, and the 3-year OS rate increases from 65% to 80%. In colorectal cancer, cetuximab combined with the FOLFOX regimen increases the ORR from 45% to 65% and the median PFS from 8 months to 12 months in patients with KRAS wild-type disease. Partial responses are still achieved in 15%-20% of patients who are resistant to FOLFOX. Target testing and monitoring for side effects are necessary. Combining chemotherapy with anti-angiogenic drugs enhances drug delivery by improving the microenvironment. Anti-angiogenic drugs can inhibit the VEGF pathway, improve vascular structure, and promote drug penetration. In advanced non-small cell lung cancer, the combination of paclitaxel + carboplatin and bevacizumab increased the ORR from 30% to 50%, extended the median PFS from 6 months to 9 months, and the median OS from 12 months to 15 months. In colorectal cancer, the combination of FOLFIRI and bevacizumab increased the median PFS from 7 months to 10 months and the median OS from 15 months to 20 months. Monitoring for toxic side effects such as hypertension and proteinuria is necessary [4].

5. APPLICATION OF IMMUNOTHERAPY IN OVERCOMING TUMOR RESISTANCE

Tumor immunotherapy activates the immune system to kill tumor cells, a mechanism significantly different from traditional chemotherapy and targeted therapy, and remains effective against drug-resistant tumors. In recent years, immune checkpoint inhibitors (ICIs) and CAR-T cell therapy have become key approaches to overcoming drug resistance. Their potential for combination with traditional treatments and the elimination of cancer stem cells (CSCs) has further expanded their application. ICIs relieve immune suppression by blocking PD-1/PD-L1 and CTLA-4, activating T cells to kill drug-resistant cells. In melanoma, approximately 50% of patients are sensitive to BRAF inhibitors but develop resistance within 6-9 months. Combining PD-1 inhibitors with these drugs increases the objective response rate (ORR) from 50% to 70%, the median progression-free survival

(PFS) from 6 months to 15 months, and the 3-year overall survival (OS) rate from 40% to 60%. For patients with non-small cell lung cancer (NSCLC) resistant to EGFR-targeted drugs, PD-1/PD-L1 inhibitors achieve an ORR of 20%-30%, and for those with PD-L1-positive tumors (TPS $\geq$ 50%), it can reach 40%-50%, with a median OS of 10-12 months, significantly superior to traditional chemotherapy. For small cell lung cancer (SCLC) resistant to chemotherapy, combining PD-L1 inhibitors with chemotherapy extends the median OS from 10 months to 12 months, and the 1-year OS rate from 30% to 50%. CAR-T cell therapy, which uses genetically modified T cells to recognize tumor antigens, is particularly effective for resistant hematologic malignancies. In children with relapsed/refractory acute lymphoblastic leukemia (ALL), CD19 CAR-T therapy achieves an ORR of 90%-95%, a complete remission (CR) rate of 80%-85%, and long-term disease-free survival in 50%-60%, far superior to traditional salvage chemotherapy [5]. In patients with diffuse large B-cell lymphoma (DLBCL), CD19 CAR-T therapy achieves an ORR of 70%-80%, a CR rate of 40%-50%, and a median OS of 12-15 months. For patients with CD19 CAR-T resistance, CD22 CAR-T therapy still achieves an ORR of 70%-80%, but caution is warranted regarding cytokine release syndrome (CRS) and neurotoxicity. Its application in solid tumors is still limited by issues such as antigenic heterogeneity. Combining immunotherapy with conventional therapies can enhance synergistic effects. In NSCLC, chemotherapy combined with PD-1 inhibitors increased ORR from 30%-40% to 60%-70%, and the median OS was extended from 12-15 months to 20-24 months; melanoma local radiotherapy combined with CTLA-4 inhibitors increased ORR from 40% to 60%, and the incidence of "remote effect" increased from 10% to 30%; BRAF inhibitors combined with PD-1 inhibitors can also significantly improve the efficacy of melanoma. In addition, immunotherapy can eliminate CSCs to block drug-resistant recurrence. Preclinical studies of breast cancer have shown that PD-1 inhibitors can reduce the proportion of CSCs from 10% to 2.% and reduced tumor recurrence rates from 80% to below 30%. In pancreatic cancer, CD44v6 CAR-T cells can specifically kill CD44v6-positive CSCs, inhibiting tumor growth and recurrence, demonstrating unique application prospects.

6. CLINICAL TRANSFORMATION OF PERSONALIZED THERAPY AND DRUG RESISTANCE MONITORING TECHNOLOGIES

Tumor drug resistance exhibits significant heterogeneity. Resistance mechanisms can vary across tumor types, patients, and even within the same patient at different stages of treatment. Therefore, personalized therapy based on individual resistance profiles is a key approach to overcoming drug resistance. Clinical translation of drug resistance monitoring technologies can dynamically track changes in resistance mechanisms, providing a basis for therapeutic adjustments. The combination of these two approaches can significantly improve treatment outcomes for patients with drug resistance. Currently, personalized therapy centers on "precise testing and matching regimens." Drug resistance monitoring has evolved from traditional tissue biopsies to minimally invasive and efficient methods such as liquid biopsies and multi-omics testing. Personalized therapy must be based on molecular testing, with treatment options tailored to the patient's molecular profile to avoid a one-size-fits-all approach. For example, in patients with advanced non-small cell lung cancer (NSCLC), testing for targets such as EGFR and ALK, and using corresponding inhibitors for mutations, can yield an objective response rate (ORR) of 60%-70% and a median progression-free survival (PFS) of 10-15 months, significantly superior to traditional chemotherapy. For patients with chemotherapy resistance, testing for molecules such as ABC transporters and Bcl-2 is recommended; those with high expression levels can improve response rates by combining them with corresponding inhibitors. For patients with colorectal cancer, testing for genes such as KRAS and NRAS is recommended; for RAS wild-type patients, combining anti-EGFR drugs with chemotherapy has shown an ORR increase from 40% to 60% and a median overall survival (OS) increase from 15 months to 20 months. Furthermore, consideration should be given to factors such as patient age and physical condition; for example, elderly patients may prefer low-toxicity targeted therapies or immunotherapies. Liquid biopsies are a key tool for drug resistance monitoring, enabling dynamic monitoring by detecting circulating tumor

DNA (ctDNA), circulating tumor cells (CTCs), and exosomes in body fluids such as blood and pleural effusions, offering minimally invasive and real-time monitoring. ctDNA can detect drug-resistant mutations such as EGFR T790M in NSCLC patients 2-6 months in advance, facilitating timely treatment adjustments. In prostate cancer, patients with CTC counts exceeding 5/7.5mL have a chemotherapy ORR of only 20%, with a median OS shortened to 10 months. Patients with high exosome expression of miR-21 in pancreatic cancer have a chemotherapy response rate of only 15%, while those with low expression reach a response rate of 45%, making it a potential indicator of drug resistance. Multi-omics testing integrates genomic and transcriptomic data to comprehensively analyze drug resistance mechanisms. For example, in ovarian cancer, drug resistance in patients with BRCA1/2 mutations is accompanied by elevated levels of ABC transporters and Bcl-2, and treatment with combination inhibitors increases the ORR from 20% to 45%. Enhanced glycolysis in drug-resistant lung cancer cells is associated with MYC amplification, and treatment with combination MYC inhibitors has an ORR of 35%-45%, which is now gradually being used in clinical practice. Transforming drug resistance monitoring requires addressing the challenges of accuracy, timeliness, and practicality: ctDNA sensitivity has reached 0.01%-0.1%, with a detection cycle of 3-5 days and decreasing costs. Some centers have established a "monitoring-adjustment" process, measuring ctDNA every 2-3 months and switching to appropriate medications based on the results. This has extended patients' median OS by 6-10 months. Future efforts to integrate AI with drug resistance prediction models could further enhance the precision of personalized treatment [6].

7. CONCLUSION

Tumor drug resistance results from the interplay of multiple factors, including abnormal intracellular drug accumulation, target mutations, inactivation of apoptotic pathways, tumor stem cell-mediated responses, and microenvironmental regulation. These interrelated mechanisms contribute to treatment tolerance, making a single strategy difficult to effectively reverse. Multi-target combination therapy based on resistance mechanisms, combined with personalized regimens and dynamic monitoring, is currently the core approach to overcoming drug resistance. Driven by molecular biology techniques, our understanding of drug resistance has evolved from single-molecule mechanisms to multi-omic network regulation. New mechanisms, such as non-coding RNAs and enhanced fatty acid metabolism in tumor cells, that contribute to chemotherapy resistance are continually being discovered. These mechanisms provide theoretical support for the development of novel strategies to reverse drug resistance and enrich the theoretical framework of drug resistance research. In clinical response, targeted drugs such as osimertinib, venetoclax, and zosuquidar have demonstrated excellent resistance-reversing effects; optimized chemotherapy regimens and combination therapy have improved prognosis by reducing resistance pressure and enhancing synergistic killing; immunotherapy is effective against traditionally resistant tumors, and combination therapy further enhances efficacy; personalized treatment, combined with ctDNA and multi-omics testing, forms a closed loop of "precision testing-treatment-adjustment," providing patients with personalized solutions. However, clinical challenges remain: some mechanisms remain unclear, immunotherapy resistance responses are limited, resistance monitoring technology is not widely available at the grassroots level, and the cost of personalized treatment is high. Future research requires focus on four key areas: analyzing novel resistance mechanisms to discover new targets, developing new drugs such as TIM-3 inhibitors and fatty acid synthase inhibitors, popularizing monitoring technologies and reducing costs, and exploring multidisciplinary collaborative diagnosis and treatment models. With in-depth research and technological advancements, the challenge of tumor resistance will be gradually resolved, providing patients with longer survival and a better quality of life.

REFERENCES

[1] Longley DB, Johnston PG. Molecular mechanisms of drug resistance [J]. Journal of Pathology: Journal of the Pathological Association of Great Britain and Ireland, 2005, 205(2): 275-292.

[2] Jiang Wenli, Zhang Lin, Li Junyao, et al. Targeted therapy of osimertinib combined with savotinib for EGFR-TKI-resistant NSCLC with MET amplification: a case report and literature review [J]. Journal of Jilin University (Medical Edition), 2023, 49(03): 782-788. DOI: 10.13481/j.1671-587X.20230330.

[3] Su Yutai, Luo Xueping, Fu Shan, et al. Observation on the efficacy of rituximab, zanubrutinib and venetoclax combined with rituximab in the treatment of diffuse large B-cell lymphoma [J]. Modern Chinese Medicine Journal, 2025, 27(03): 8-13.

[4] Garg P, Malhotra J, Kulkarni P, et al. Emerging therapeutic strategies to overcome cancer cell resistance [J]. Cancer, 2024, 16(13): 2478.

[5] Bai R, Chen N, Li L, et al. Cancer resistance of immunotherapy [J]. Frontiers in oncology, 2020, 10: 1290.

[6] Wu Jian, Lin Zhe. Targeted therapy for non-small cell lung cancer: drugs and resistance mechanisms [J]. International Journal of Molecular Sciences, 2022, 23(23): 15056.