Middle Eastern Cancer and Oncology Journal (MECOJ)
ISSN: 3080-1427 (online) / 3080-1419 (print)
Volume 1, Issue 3 (July 2025 – September 2025), pp: 24-32

Review Article

Mechanisms of Chemoresistance in Solid and Hematologic Malignancies: Challenges and Future Perspectives

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Received: 16 June 2025 | Revised: 19 August 2025 | Accepted: 17 September 2025 | Published: 24 September 2025

Abstract

Chemotherapy is a foundational element in cancer therapy; however, the development of resistance to antineoplastic agents presents a significant challenge to achieving enduring therapeutic triumphs. The acquisition of drug resistance by malignant cells is the result of a complex interplay between inherent and acquired mechanisms. This phenomenon leads to a reduction in pharmacological effectiveness and contributes to treatment failure. This review investigates the primary mechanisms contributing to chemoresistance in specific malignancies, namely lung, pancreatic, and thyroid cancers, along with non-Hodgkin lymphoma. The primary focus of this research is on genetic modifications, interactions within the tumor microenvironment, and cellular adaptations at the molecular level. The present study places particular emphasis on the contributions of drug efflux pumps, DNA repair pathways, epithelial-mesenchymal transition (EMT), microRNAs, and the suppression of apoptosis in mediating this resistance. In addition, we examine promising approaches to counteract drug resistance, encompassing multi-agent regimens, inhibitors targeting specific molecular pathways, and innovative therapeutic modalities. A comprehensive understanding of these fundamental mechanisms is imperative for the development of sophisticated therapeutic interventions that not only improve patient outcomes but also effectively address resistance. The resistance pathways and prospective translational approaches discussed are drawn from both preclinical and clinical investigations, providing a thorough perspective. Keywords: The following terms are relevant to the study: chemoresistance, tumor microenvironment, molecular pathways, targeted therapy, and resistance mechanisms.

Keywords: *Chemoresistance, Tumor Microenvironment, Molecular Pathways, Targeted Therapy, Resistance Mechanisms.*

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Cite This Article: Batlamous, B., Elgharbaoui, B., Bensalim, I., & Khalis, M. (2025). Mechanisms of Chemoresistance in Solid and Hematologic Malignancies: Challenges and Future Perspectives. *Middle Eastern Cancer and Oncology Journal*, *1*(3), 24-32. https://doi.org/10.61706/MECOJ160161

Introduction

Cancer is distinguished by its substantial heterogeneity, which is driven by a multitude of genetic and molecular alterations that initiate and progress the disease. The hallmarks of malignancy are a set of characteristics that are associated with the development of cancer. These hallmarks include uncontrolled cellular proliferation, the ability to evade growth suppressors, and programmed cell death (apoptosis). Additionally, new blood vessel formation (angiogenesis), spread to distant sites (metastasis), and unchecked replicative potential are also hallmarks of malignancy. Recent advancements in the field have identified additional hallmarks, including cellular senescence in cancer, evasion of immune surveillance, chronic inflammation, genomic instability, metabolic dysregulation, phenotypic adaptability, epigenetic alterations, the influence of polymorphic microbes, and further levels of epigenetic reprogramming. These attributes, particularly genomic instability, phenotypic plasticity, and immune evasion, not only facilitate cancer advancement but also present substantial obstacles to successful chemotherapy. For instance, substantial intratumoral heterogeneity and aberrant survival signaling pathways can compromise the effectiveness of pharmaceutical agents, thereby fostering both intrinsic and acquired resistance to chemotherapy (Hanahan, 2022; Kar et al., 2024).

Conventional cancer therapeutic modalities encompass chemotherapy, radiotherapy, and surgical intervention. Furthermore, contemporary strategies, including immunotherapy and targeted therapies, have become integral components of clinical practice (de Moura et al., 2023). Despite its frequent use as a primary treatment modality in conjunction with surgery and radiation, the emergence of resistance mechanisms frequently necessitates second-line chemotherapy following initial treatment failure. In instances where tumors exhibit resistance or disease progression following initial treatment, clinicians must contemplate alternative pharmaceuticals or combination regimens, with the occasional incorporation of immunotherapy (de Moura et al., 2023). Nevertheless, irrespective of its role as a primary or secondary treatment, chemotherapy frequently elicits severe adverse effects due to its non-selective mechanism, manifesting as nausea, emesis, gastrointestinal discomfort, anemia, and chemotherapy-induced peripheral neuropathy, among other deleterious outcomes (Nurgali et al., 2018). Specific approaches, such as modulating chemotherapy dosing via intermittent or intensified schedules, in conjunction with supportive agents and growth factors to safeguard bone marrow, have demonstrated efficacy in preventing tumor recurrence. Despite these efforts, resistance to chemotherapy remains a significant impediment in the field of oncology. Consequently, a comprehensive understanding of both intrinsic and acquired mechanisms of resistance is imperative for the development of future targeted therapies (DeRidder et al., 2022; Miglietta et al., 2023; Xu et al., 2023).

The development of cancer resistance to chemotherapeutic agents is the result of intricate interactions between intrinsic (inherent) and extrinsic (environmental) elements. Intrinsic resistance has been shown to originate from diverse factors, including tumor heterogeneity, the activation of internal cellular defense pathways, pre-existing genetic alterations, the activation of oncogenic pathways, diminished sensitivity of drug targets, DNA repair mechanisms, and hyperactive survival signaling pathways (Dzobo et al., 2018; Khan et al., 2024; Labrie et al., 2022). Concurrently, external factors, particularly components within the tumor microenvironment (TME), empower cancer cells to circumvent the cytocidal effects of therapeutic agents (Labrie et al., 2022). A number of distinct malignancies, including lung, pancreatic, and thyroid cancers, as well as non-Hodgkin lymphoma, exhibit substantial chemoresistance. This review is specifically focused on the mechanisms of resistance within these particular cancer types.

Lung Cancer

On a global scale, lung cancer persists as a predominant cause of cancer-related mortality, responsible for an estimated 1.8 million annual deaths. This neoplasm is generally classified into two distinct categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Non-small cell lung cancer (NSCLC) accounts for the majority of cases (85%) and is further subdivided into adenocarcinoma (LUAD), squamous cell carcinoma (LUSC), and large cell carcinoma (LCLC). SCLC constitutes the remaining 15% of lung cancer diagnoses (Bade & Dela Cruz, 2020; Chaitanya Thandra et al., 2021; de Sousa & Carvalho, 2018; Hua et al., 2020; Marino et al., 2019). Despite the growing enthusiasm for targeted therapeutic approaches, chemotherapy continues to be a cornerstone treatment, particularly for advanced or surgically unresectable NSCLC, and is utilized as both

first- and second-line therapy for SCLC. The primary classes of chemotherapeutic agents employed include alkylating compounds (e.g., cisplatin, carboplatin), microtubule-disrupting agents (e.g., paclitaxel, docetaxel, vinorelbine), antimetabolites, and topoisomerase inhibitors. However, a prevalent clinical predicament is the emergence of chemoresistance in tumors following an initial positive response to chemotherapy (Janet Wangari-Talbot & Elizabeth Hopper-Borge, 2013; Jordan & Wilson, 2004; Konstantinov & Berger, n.d.; Min & Lee, 2021; Olaussen & Postel-Vinay, 2016; Yuan et al., 2019).

The mechanisms driving chemoresistance in lung cancer are diverse and include alterations in drug efflux and influx, modifications to drug targets, epigenetic alterations, enhanced DNA damage repair, evasion of apoptosis, epithelial-mesenchymal transition (EMT), acquisition of cancer stem cell-like characteristics, aberrant microRNA (miRNA) regulation, and complex interactions with the tumor microenvironment (TME). It is important to note that these mechanisms frequently do not operate in isolation, but rather synergistically. For instance, an increase in ABC transporter expression can lower intracellular drug concentrations while concurrently impeding apoptotic pathways, thereby exacerbating resistance. Conversely, the activation of DNA damage repair pathways may enable cancer cells to withstand cytotoxic insults, while EMT fosters cellular plasticity and stemness, further promoting drug tolerance. The TME, a complex milieu of fibroblasts, immune cells, endothelial cells, extracellular matrix components, and intricate vasculature, has been shown to promote tumor progression by inducing conditions such as hypoxia and nutrient deprivation, along with fostering increased vascular density (Assaraf et al., 2019; Bukowski et al., 2020; Chen et al., 2020; Holohan et al., 2013; Housman et al., 2014; Kim & Lee, 2017; Ramos et al., 2021; Riganti & Contino, 2019).

Research indicates that resistance to platinum-based chemotherapy is often mediated by the activation of DNA repair mechanisms, specifically homologous recombination (HR) and nucleotide excision repair (NER). In non-small cell lung cancer (NSCLC), resistance to cisplatin has been associated with elevated levels of excision repair cross-complementing 1 (ERCC1), a critical component of the nucleotide excision repair (NER) pathway. ATP-binding cassette (ABC) transporters play a pivotal role in the regulation of drug transport, and their expression, including members such as MRP1/ABCC1 and MRP3/ABCC3, is associated with drug resistance. It is noteworthy that a significant proportion of non-small cell lung cancer (NSCLC) cells that develop resistance to paclitaxel, docetaxel, or vinorelbine frequently exhibit heightened expression of ABCB1/MDR1/p-glycoprotein, ABCC3/MRP3, and ABCC10/MRP7 (Bessho et al., 2009; Cui et al., 2020; Oguri et al., 2008; Shen et al., 2014; SHIMOMURA et al., 2012; Young et al., 2001; Zhao et al., 2013).

Furthermore, the elevated expression of glutathione S-transferase (GSTP1) and glutathione S-transferase alpha 1 (GSTA1) contributes to the inactivation of platinum-based drugs, leading to chemoresistance. Patients presenting with elevated GSTP1 levels exhibit suboptimal responses to cisplatin. Furthermore, studies have demonstrated that the inhibition of GSTP can enhance the sensitivity of cancer cells to chemotherapy agents such as doxorubicin, cisplatin, and etoposide (Holohan et al., 2013; Pljesa-Ercegovac et al., 2018; A. Sharma et al., 2006; C.-Y. Sun et al., 2019; Townsend & Tew, 2003).

Pancreatic Cancer

Projections indicate that pancreatic cancer will become the second leading cause of cancer-related mortality by the year 2030. On a global scale, the year 2018 saw 458,918 new diagnoses and 432,242 deaths from pancreatic cancer (44–50). Despite advancements in diagnostic techniques and therapeutic interventions, the five-year survival rate for this cancer remains low, at approximately 9% (Chonghaile & Letai, 2008; Geisslinger et al., 2020; Inno et al., 2018; R. Liu et al., 2020; Lok et al., 2017; Pearce et al., 2018; Reshma et al., 2019; Stewart, 2007; Sun et al., 2018; Thomas et al., 2013). Pancreatic ductal adenocarcinoma (PDAC) constitutes 90% of all pancreatic malignancies (Ansari et al., 2016; Kamisawa et al., 2016; Kaur et al., 2017; Kleeff et al., 2016; Rahib et al., 2014; Rawla et al., 2019; Si et al., 2019; Siegel et al., 2018; Wang et al., 2020; Zagryazhskaya & Zhivotovsky, 2014; Zhou et al., 2018).

Advanced pancreatic cancer frequently demonstrates invasion into adjacent tissues and distant metastasis, substantially diminishing patient survival prospects. A primary factor contributing to the unfavorable prognosis of pancreatic cancer is its resistance to chemotherapy. The underlying factors contributing to this phenomenon include genetic and molecular modifications affecting intracellular signaling, DNA repair mechanisms, cellular metabolism, and the regulation of replication (Nassar & Blanpain, 2016; Quiñonero et al., 2019).

Thyroid Cancer

Thyroid cancer is the most prevalent endocrine malignancy, with a marked increase in incidence observed over recent decades (Espona-Fiedler et al., 2024; Seib & Sosa, 2019; Siegel et al., 2019; Sung et al., 2021; Zhang et al., 2022). The continuous advancements in medical technology have contributed

to the sustained increase in thyroid cancer diagnoses (Liu, 2025).

A primary metabolic mechanism contributing to chemoresistance involves the enhanced efflux of therapeutic agents facilitated by ATP-binding cassette (ABC) transporters. These transmembrane proteins are evolutionarily conserved pumps that safeguard cells by inhibiting the intracellular accumulation of toxic compounds. Specific ABC family members, including multidrug resistance protein 1 (MDR1), multidrug resistance-associated protein 1 (MRP1), and breast cancer resistance protein (BCRP), have been identified as the transporters responsible for the efflux of numerous xenobiotics, including kinase inhibitors, from cells (Abbasifarid et al., 2019). For instance, kinase inhibitors such as sorafenib and lenvatinib, which are frequently utilized in the management of advanced thyroid cancer, have been identified as substrates for efflux transporters including MDR1 and BCRP. Elevated expression of these transporters has been demonstrated to result in reduced intracellular drug concentrations, which can subsequently lead to treatment failure. Furthermore, studies have demonstrated a correlation between resistance to sorafenib and the upregulation of components within the MAPK pathway, as well as genes associated with epithelial-mesenchymal transition (EMT) (Wu et al., 2019). The expression of EMT-related genes, such as Snail-1, plays a significant role in the genesis of cancer stem cells (CSCs) and in the emergence of chemoresistance within thyroid cancer cells. This can lead to disease recurrence at the primary tumor site or in distant organs, necessitating highly effective therapeutic strategies (Cuomo et al., 2022).

Non-Hodgkin Lymphoma

On a global scale, non-Hodgkin lymphoma (NHL) is recognized as the eleventh most frequently diagnosed cancer. In 2020, the number of newly reported cases of non-Hodgkin's lymphoma (NHL) was 544,352, and the number of deaths attributed to NHL was 259,793. Despite the observed decline in mortality rates, NHL persists in its capacity to impose a considerable health burden (Cai et al., 2021; Klener & Klanova, 2020; Mukhtar et al., 2018).

A total of 90 distinct subtypes of NHL have been identified, each exhibiting unique biological behaviors and varied responses to treatment. While the advent of targeted therapies has led to an enhancement in survival rates, the challenge of overcoming treatment resistance persists as a significant impediment. The mechanisms of chemoresistance in non-Hodgkin lymphoma (NHL) encompass two distinct phenomena. The first is intrinsic resistance, in which lymphoma cells inherently lack the expression of specific therapeutic targets. For example, CD20-negative lymphomas may not respond to rituximab. The second is acquired resistance, which occurs when tumors initially react favorably to treatment but subsequently develop an unresponsive phenotype. Recent findings have highlighted mechanisms that contribute to resistance to CAR-T cell therapy beyond the conventional chemotherapy and monoclonal antibodies. These mechanisms include the loss of target antigens (e.g., CD19 downregulation), the presence of immunosuppressive tumor microenvironments, and T cell exhaustion. These elements impose constraints on the sustained effectiveness of CAR-T cell responses and signify pivotal domains for future research endeavors. Furthermore, factors such as tumor heterogeneity and the existence of drug-tolerant persister (DTP) cells contribute to both resistance and disease relapse (Jiang et al., 2014; Juskevicius et al., 2016; Russo et al., 2019; Schürch et al., 2018; Sharma et al., 2010).

Conclusion

Chemoresistance poses a substantial obstacle to effective cancer therapy, often resulting in disease progression and diminished patient prognoses. The underlying mechanisms are diverse and complex, involving genetic modifications, active drug efflux, suppression of apoptosis, epithelial-mesenchymal transition (EMT), and intricate interactions within the tumor microenvironment (TME). The development of strategies that target these resistance pathways, such as the employment of combination therapies, specific targeted inhibitors, and innovative therapeutic modalities, offers considerable potential for mitigating treatment failure. Future investigations should prioritize the discovery of reliable predictive biomarkers. Such biomarkers may include genomic indicators, such as epidermal growth factor receptor (EGFR) mutations or breast cancer susceptibility gene (BRCA) status, epigenetic changes, such as promoter methylation, and distinct proteomic profiles. These biomarkers could aid in classifying patients based on their anticipated treatment response. The incorporation of these biomarkers into individualized treatment plans will be essential for overcoming resistance and enhancing the precision of therapeutic interventions.

Declarations

Ethics approval and consent to participate

Not applicable – no participants involved.

Consent for Publication

Not applicable.

Availability of Data and Material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Conflicts of Interest / Competing Interests

The authors declare that there are no conflicts of interest.

Funding

The authors declare that this research received no external funding.

Author Contributions

B. B: Writing of the original draft, Writing – review & editing.

B. E: Writing of the original draft, Writing – review & editing.

I. B: Writing of the original draft, Writing – review & editing.

M. K: Conceptualization, Methodology, Supervision.

Acknowledgment

Not applicable

Use of Generative AI and AI-Assisted Technologies

The authors declare that no generative AI or AI-assisted technologies were used in the preparation of this work.

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