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Review paper

Overcoming Multidrug Resistance: Molecular Insights into Strategies for Effective Cancer Drug Delivery

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Abstract

Background and aim: Multidrug resistance (MDR) remains an obstacle in cancer treatment. This review paper aims to provide a comprehensive overview of the molecular mechanisms underlying MDR in cancer and to explore innovative strategies for enhancing drug delivery to overcome this challenge. Our goal is to elucidate the latest molecular insights that can inform the development of more effective therapeutic approaches.

Methods: We conducted an extensive literature search using online databases such as PubMed, Web of Science, and Scopus. Key terms included "multidrug resistance," "cancer drug delivery," "molecular mechanisms," and related variations. Articles published from 2015 to 2023 were considered to ensure coverage of recent developments. The inclusion criteria encompassed studies focusing on molecular mechanisms of MDR in cancer, innovative drug delivery strategies, and relevant preclinical and clinical outcomes. We excluded articles that were not available in English.

Results: Our analysis highlights the intricate network of molecular mechanisms contributing to MDR in cancer. We discuss the potential of combination therapies targeting MDR-associated pathways and the promising results of preclinical and clinical studies. Moreover, we present advancements in drug delivery systems that enhance drug stability, circulation time, and selective targeting of cancer cells, thereby mitigating MDR.

Conclusion: Molecular insights into the mechanisms of MDR offer opportunities for the development of targeted therapies that can sensitize drug-resistant cancer cells. Innovative drug delivery systems provide a means to improve drug pharmacokinetics and tumor-specific delivery, enhancing therapeutic efficacy. Combining these approaches holds great promise in the battle against MDR in cancer treatment.

Keywords: *Multidrug resistance, Cancer, Drug Delivery, Molecular Mechanisms, Therapeutic Strategies*

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Introduction

Cancer, a complex and devastating group of diseases characterized by uncontrolled cell growth and invasive tendencies, remains a significant global health challenge. Its occurrence is influenced by a combination of genetic, environmental, and lifestyle factors, resulting in diverse manifestations across various organs. Significant strides have been achieved in the field of cancer treatment, marking a transformative era in the battle against this formidable disease. Over the past decades, advancements in scientific research, medical technology, and therapeutic strategies have collectively propelled the oncology landscape forward. These breakthroughs encompass a spectrum of innovations, ranging from novel drug development and targeted therapies to precision medicine approaches that consider the unique genetic signatures of individual tumors. However, despite these advances, cancer continues to exert a substantial socio-economic toll, impacting individuals, families, and healthcare systems worldwide. The imperative to innovate and enhance treatment approaches is underscored by the increasing incidence of cancer, demographic changes, and evolving risk factors [1], [2], [3], [4].

Multidrug resistance (MDR) refers to the ability of cancer cells, or other microorganisms, to develop resistance to multiple drugs, rendering them less susceptible to the effects of various therapeutic agents. In the context of cancer, MDR is a significant obstacle to successful chemotherapy. Cancer cells may evolve mechanisms to efflux drugs out of the cell, decrease drug uptake, or develop alterations in drug targets, all of which contribute to the reduced effectiveness of chemotherapy. MDR is a complex and dynamic phenomenon, often involving multiple cellular pathways and mechanisms, making it challenging to overcome. Understanding and addressing multidrug resistance is crucial for improving the outcomes of cancer treatment and developing more effective therapeutic strategies [5].

MDR in cancer involves a complex interplay of diverse mechanisms that collectively diminish the effectiveness of multiple therapeutic agents. Key mechanisms include the upregulation of ATP-binding cassette (ABC) transporters, such as P-glycoprotein, leading to increased drug efflux, and alterations in membrane transporters affecting drug uptake. Additionally, MDR can result from enhanced drug metabolism, changes in drug target expression or functionality, resistance to apoptosis, upregulation of DNA repair mechanisms, and the influence of microenvironmental factors and epigenetic changes. The existence of cancer stem cells with inherent resistance adds another layer to MDR complexity [6].

MDR in cancer presents a formidable obstacle, significantly impeding the success of therapeutic approaches and diminishing the overall effectiveness of various anticancer treatments. This intricate phenomenon, where cancer cells develop resistance to multiple chemotherapeutic agents, involves a complex interplay of genetic, epigenetic, and microenvironmental factors. Despite the substantial strides made in cancer research and the development of diverse anticancer drugs, the persistent emergence of MDR poses a continual challenge to achieving optimal treatment outcomes. The adaptability and evolution of cancer cells, enabling them to resist the effects of multiple drugs through various mechanisms, underscore the complexity of MDR. This phenomenon necessitates a deeper exploration of the underlying molecular pathways to develop strategies that can overcome or circumvent drug resistance [7], [8].

This study addresses the critical necessity of understanding and MDR in cancer treatment. Despite advancements in drug development, MDR remains a significant hurdle, limiting therapeutic efficacy. The review aims to fill a gap in the existing literature by providing a consolidated resource that integrates molecular insights into practical strategies for enhancing drug delivery specifically within the context of MDR. By synthesizing current knowledge, the paper aims to

guide future research efforts toward more effective and targeted approaches in cancer therapy, fostering advancements that can improve treatment outcomes.

Methods

A systematic approach is employed, utilizing key terms such as multidrug resistance, cancer drug delivery, and molecular mechanisms. The search is conducted on reputable platforms such as Google Scholar, PubMed, and Clarivate Analytics. Inclusion criteria prioritize peer-reviewed articles in English that are focused on multidrug resistance in cancer, providing molecular insights into resistance mechanisms, and discussing strategies for effective drug delivery, including nanoparticle and targeted therapy approaches. Exclusion criteria are applied to filter out non-English publications, non-peer-reviewed sources, and studies lacking relevance to the molecular understanding or practical strategies of drug delivery.

Literature Review

In 2015, a study outlined various strategies employed in both preclinical and clinical settings to address cancer multidrug resistance (MDR), including the use of chemosensitizers to sensitize cancer cells to chemotherapy and the utilization of nanomedicines as delivery vehicles to enhance drug influx into cancer cells, thereby improving therapeutic response in resistant tumors [9]. A review study in the same year focused on overcoming multidrug resistance in cancer stem cells, discussing strategies such as competitive and allosteric modulators, nanoparticle-mediated delivery of inhibitors, targeted transcriptional regulation of ABC transporters, miRNA-mediated inhibition, and targeting signaling pathways modulating ABC transporters [10]. Dinic et al. (2015) emphasized the role of numerous genes and pathways in the development of MDR in cancer, highlighting genetic and epigenetic changes, abnormal tumor vasculature, hypoxia, aerobic glycolysis, and decreased susceptibility to apoptosis as key features. The overexpression of the efflux transporter P-glycoprotein (P-gp) in MDR cancer cells was identified as a critical factor leading to decreased drug uptake and intracellular drug accumulation [11]. A review by Beretta et al. (2016) discussed various nanovectors designed for efficient delivery of anticancer drugs and their role in overcoming MDR, addressing challenges and opportunities for further development of nanodevices-based chemotherapies [12]. Another review in 2016 focused on the current literature in nanomedicine for solid cancers and the potential treatment of multidrug-resistant cancers, emphasizing the need for a deeper understanding of receptor interactions, nanomedical construct physics, and circulation in the body [13].

In 2017, Zhang et al. highlighted combination therapy as an effective strategy for overcoming MDR, discussing nanotechnology-based codelivery techniques that offer advantages for tumor targeting, controlled drug release, and identical drug pharmacokinetic profiles [14]. A review in the same year explored novel strategies to prevent the development of MDR in cancer, emphasizing the importance of preventing MDR at the onset of chemotherapy treatment to improve therapeutic efficacy and patient outcomes [15]. Cui et al. (2018) discussed modulating reactive oxidative species (ROS) as an approach to reverse MDR in cancer cells, pointing out that compounds modulating cellular ROS levels hold promise for enhancing MDR cancer cell death and sensitizing them to chemotherapeutic drugs [16]. In another 2018 review, the focus was on polymeric micelles to overcome MDR in tumors, emphasizing the need for fundamental research to study the underlying mechanisms and conduct preclinical/clinical testing of micellar formulations [17].

A 2019 review highlighted the complexity of MDR in cancer chemotherapy, emphasizing strategies to increase drug delivery into cancer cells, such as the inhibition of carbonic anhydrases and modulation of MDR proteins [18]. Ye et al. (2019) summarized the potential of flavonoids to overcome MDR, discussing their multi-functional role in negatively regulating key factors contributing to MDR [19]. In 2020, Majidinia et al. focused on nano-drug delivery systems, including various nanoparticles, to overcome the mechanisms of MDR and improve therapeutic efficacy in anticancer treatments [20]. A study in the same year reviewed drugs targeting MDR and cancer stem cells, discussing limitations and future perspectives [21]. M.F. Gonçalves et al. (2020) highlighted natural product-derived compounds, particularly flavonoids and terpenoids, as promising modulators of ABC transporters to tackle MDR [22].

In 2021, El-Readi et al. underscored the potential of plant secondary metabolites to overcome MDR in cancer, highlighting their multi-molecular mechanisms, including interaction with membrane proteins and induction of apoptosis [23]. Duan et al. (2021) reviewed the recent progress of nanomaterials in medicine, discussing the application of liposomal nanoparticles, polymeric nanoparticles, inorganic nanoparticles, and hybrid nanoparticles to overcome cancer multidrug resistance [24]. Another 2021 review focused on nanotechnology-based drug delivery platforms to enhance the efficiency of chemotherapy and overcome MDR in a synergistic manner, detailing different combinatorial strategies [25]. Majerník (2022) discussed the application of photodynamic therapy (PDT) in overcoming MDR, emphasizing the potential of nanoparticles to enhance therapeutic efficacy [26]. A 2022 study summarized the mechanisms of drug resistance and nanoparticle-based strategies to combat drug resistance in cancer, highlighting the potential of gene therapy and natural substances [27]. Vaidya et al. (2022) emphasized the need for an improved understanding of the molecular mechanisms of MDR and cellular reprogramming to combat drug resistance in cancer [28].

In a 2023 study, Duan et al. provided a comprehensive overview of reasons, mechanisms, nanotherapeutic solutions, and challenges in overcoming cancer MDR, discussing drug efflux mechanisms, reduced drug uptake, altered DNA repair, and drug targets [29]. Zhang et al. (2023) delved into the molecular mechanisms associated with MDR in cancers, covering protein–protein interactions, alternative splicing, non-coding RNA mediation, genome mutations, variance in cell functions, and tumor microenvironment influence [30].

Discussion

The complex area of study involves the persistent challenge of MDR in cancer therapy, with molecular insights into strategies for effective drug delivery being offered. Emphasizing the complexity of MDR, which includes diverse genetic, epigenetic, and microenvironmental factors, the continuous impediment it poses to optimal treatment outcomes should be underscored despite significant advancements in cancer research [31]. Through a systematic review of a wealth of literature, the evolution of innovative strategies, such as the use of chemosensitizers, nanomedicines, and modulation of reactive oxidative species, is traced by the authors, providing a chronological perspective on the dynamic landscape of MDR research [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [32]. The significance of molecular understanding in overcoming MDR is highlighted, emphasizing the adaptability and evolution of cancer cells as key factors necessitating a deeper exploration of underlying pathways. A promising avenue to enhance drug delivery precision emerges with the incorporation of nanotechnology-based approaches and combination therapies. Overall, existing knowledge is not only consolidated, but a strategic

direction for future research is also set, guiding efforts towards more targeted and effective cancer therapies.

Conclusion

In-depth understanding of the molecular mechanisms underlying multidrug resistance (MDR) presents a valuable foundation for the exploration and development of targeted therapies designed to sensitize drug-resistant cancer cells. The intricate knowledge gained from molecular insights allows for the identification of specific vulnerabilities and resistance mechanisms within cancer cells, paving the way for more precise and effective interventions. Concurrently, the advent of innovative drug delivery systems has emerged as a pivotal strategy to address the challenges posed by MDR. These advanced delivery systems not only optimize drug pharmacokinetics but also facilitate tumor-specific delivery, thereby augmenting therapeutic efficacy. By synergistically combining the molecular insights into MDR mechanisms with state-of-the-art drug delivery technologies, a powerful and comprehensive approach can be formulated. This combined strategy holds great promise in revolutionizing cancer treatment by overcoming the formidable barrier of MDR, offering new avenues for therapeutic success and improved patient outcomes.

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Conflict of interests

The authors declare no conflicts of interest.

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