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Nanomedicine in Overcoming Chemoresistance: Mechanistic Insights and Therapeutic Opportunities

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ABSTRACT

Chemoresistance remains a formidable challenge in cancer therapy, often leading to treatment failure, disease relapse, and poor patient prognosis. Traditional chemotherapy is limited by non-specific toxicity, multidrug resistance (MDR), and inefficient drug delivery to tumor tissues. Nanomedicine offers a promising approach to address these limitations by enabling targeted, controlled, and stimuli-responsive delivery of chemotherapeutic agents. This review provides a comprehensive overview of the mechanisms underlying chemoresistance, including drug efflux via ATP-binding cassette (ABC) transporters, altered drug metabolism, DNA damage repair, tumor heterogeneity, epithelial-to-mesenchymal transition (EMT), and the role of the tumor microenvironment. We then explore how nanomedicine strategies ranging from liposomes, polymeric nanoparticles, dendrimers, and micelles to more advanced stimuli-responsive and multifunctional platforms can be designed to overcome these resistance pathways. Special emphasis is placed on co-delivery systems targeting MDR proteins, nanocarriers for gene silencing (e.g., siRNA, miRNA), and tumor-penetrating nanostructures that bypass stromal barriers. Furthermore, the review discusses recent advances in biomimetic and smart nanocarriers that respond to tumor-specific cues (e.g., pH, enzymes, redox conditions) to enhance drug bioavailability and therapeutic efficacy. Clinical progress, regulatory considerations, and future perspectives on integrating nanomedicine with personalized therapy and immunomodulation are also highlighted. Overall, nanomedicine holds transformative potential to reshape the landscape of cancer treatment by effectively overcoming chemoresistance and improving patient outcomes.

Keywords: Chemoresistance, Nanomedicine, Drug Delivery, Tumor Microenvironment, Multidrug Resistance

INTRODUCTION

Chemotherapy has long been a cornerstone in the treatment of various malignancies and continues to serve as a primary therapeutic modality for numerous cancer types, including breast, lung, ovarian, and colorectal cancers[1–4]. Despite its widespread application and initial success in reducing tumor burden, the long-term effectiveness of chemotherapy is frequently undermined by the emergence of chemoresistance[5–8]. Chemoresistance may be either intrinsic, where cancer cells are inherently unresponsive to chemotherapeutic agents, or acquired, developing over the course of treatment due to selective pressures exerted by prolonged drug exposure[9–11]. In both scenarios, resistance significantly limits therapeutic efficacy, leading to disease progression, tumor relapse, and poor clinical outcomes. The mechanisms underlying chemoresistance are complex and multifactorial, encompassing genetic, epigenetic, and biochemical alterations within tumor cells and the surrounding tumor microenvironment. Commonly encountered resistance pathways include increased drug efflux mediated by ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp); enhanced DNA repair capacity; alterations in drug targets; epithelial-mesenchymal transition (EMT); evasion of apoptosis; and metabolic reprogramming[12]. Additionally, the immunosuppressive tumor microenvironment, hypoxia, and the presence of cancer stem cells (CSCs) further exacerbate resistance, rendering standard chemotherapeutic regimens less effective. These adaptations enable cancer cells to survive even in the presence of cytotoxic agents, thereby challenging sustained remission and long-term patient survival[13].

Conventional approaches to combat chemoresistance have primarily relied on increasing the dose of chemotherapeutic agents or employing combination therapies involving multiple drugs with distinct mechanisms of action[14]. However, such strategies are not without limitations. Dose escalation often leads to severe systemic toxicity, negatively impacting the patient's quality of life and causing damage to healthy tissues

and organs. Meanwhile, combination therapy, although somewhat effective, is frequently associated with increased treatment complexity, unpredictable pharmacokinetics, and the potential for drug–drug interactions. These challenges underscore the need for more refined and targeted approaches that can effectively circumvent chemoresistance while minimizing adverse effects[14].

In this context, nanomedicine has emerged as a transformative tool in oncology, offering innovative strategies to enhance the delivery and efficacy of chemotherapeutic agents[15–18]. Nanomedicine refers to the medical application of nanotechnology, which involves the design and use of materials and devices at the nanoscale typically ranging from 1 to 100 nanometers for diagnostic, therapeutic, and monitoring purposes[3, 19–21]. Nanocarriers, such as liposomes, polymeric nanoparticles, dendrimers, micelles, and inorganic nanoparticles (e.g., gold or silica-based), can be engineered to encapsulate anticancer drugs, improving their solubility, stability, and bioavailability[15, 22–24].

One of the most significant advantages of nanomedicine is its ability to exploit the enhanced permeability and retention (EPR) effect, a phenomenon whereby nanoparticles preferentially accumulate in tumor tissues due to the leaky vasculature and impaired lymphatic drainage commonly observed in tumors[24–27]. This passive targeting, combined with active targeting strategies involving surface modification with ligands (e.g., antibodies, peptides, or aptamers) that bind to tumor-specific receptors, enables highly selective drug delivery to cancer cells while sparing normal tissues. Furthermore, nanocarriers can be designed to respond to specific stimuli such as pH, redox potential, or enzymes within the tumor microenvironment, allowing for controlled and site-specific drug release[28–30].

Crucially, nanotechnology also enables co-delivery systems, where multiple therapeutic agents can be loaded into a single nanocarrier. This capability allows for the simultaneous delivery of traditional chemotherapeutics alongside agents that modulate resistance mechanisms, such as siRNA to silence drug-resistance genes, inhibitors of efflux pumps, or compounds that sensitize cancer cells to apoptosis[19, 31–33]. Such combinatorial approaches can effectively neutralize key resistance pathways, thereby restoring chemosensitivity and improving overall therapeutic outcomes.

In sum while chemoresistance remains a formidable obstacle in cancer therapy, the advent of nanomedicine offers a promising frontier for developing next-generation treatments. Through precise tumor targeting, controlled drug release, and the ability to bypass or directly inhibit resistance mechanisms, nanotechnology holds significant potential to revolutionize how we approach drug-resistant cancers. This review aims to provide a comprehensive overview of the molecular underpinnings of chemoresistance and explore how nanomedicine-based strategies can be harnessed to overcome these challenges, thereby paving the way for more effective and personalized cancer therapies.

2. Mechanisms of Chemoresistance

2.1 Efflux Pumps and Drug Transport: Efflux pumps, particularly those belonging to the ATP-binding cassette (ABC) transporter family, play a pivotal role in multidrug resistance in cancer cells[34, 35]. These transmembrane proteins use the energy derived from ATP hydrolysis to actively export chemotherapeutic agents out of cells, thereby reducing intracellular drug accumulation and limiting cytotoxic effects. Among the most studied efflux pumps are P-glycoprotein (P-gp, encoded by the *ABCB1* gene), multidrug resistance-associated protein 1 (MRP1), and breast cancer resistance protein (BCRP). These transporters are often upregulated in drug-resistant tumor cells and contribute to both intrinsic and acquired resistance[36]. Overexpression of these efflux pumps has been documented in various malignancies, including breast cancer, leukemia, and colon cancer. Their broad substrate specificity enables them to efflux structurally diverse compounds such as taxanes, anthracyclines, and vinca alkaloids. Inhibitors of ABC transporters have been investigated as adjuvants to chemotherapy, but clinical success has been limited due to toxicity and off-target effects. Recent advances in nanomedicine and targeted delivery systems aim to bypass or inhibit efflux activity selectively within tumor tissues.[37] Understanding the regulation and function of these transporters is critical for designing more effective strategies to overcome chemoresistance and improve therapeutic efficacy in cancer treatment.

2.2 Drug Inactivation: Drug inactivation through metabolic modification is another crucial mechanism by which cancer cells develop resistance to chemotherapy. Enzymes such as glutathione S-transferases (GSTs), cytochrome P450 oxidases (CYPs), and aldehyde dehydrogenases (ALDHs) play significant roles in neutralizing anticancer agents[38]. These enzymes catalyze the conjugation, oxidation, or reduction of chemotherapeutic drugs, rendering them inactive or facilitating their excretion[38]. For example, GSTs catalyze the conjugation of glutathione to electrophilic compounds, including alkylating agents and platinum-based drugs, which impairs their ability to damage DNA or cellular structures[39]. Overexpression of specific CYP enzymes, such as CYP3A4, may accelerate the breakdown of drugs like paclitaxel and cyclophosphamide, thereby diminishing their therapeutic impact. In addition, some tumor cells upregulate phase II detoxifying enzymes in response to chemotherapy as a form of adaptive resistance[40]. This enzymatic defense system not only detoxifies drugs

but can also generate harmful byproducts that promote further genetic instability. The upregulation of these enzymes is often regulated by transcription factors like NRF2, which governs the oxidative stress response. Targeting drug-metabolizing enzymes or their regulators offers a promising avenue for overcoming resistance and enhancing the efficacy of chemotherapy.

2.3 Altered Drug Targets: Alterations in drug targets represent a central mechanism by which cancer cells evade the cytotoxic effects of chemotherapeutic agents[41]. These changes can occur through mutations, alternative splicing, post-translational modifications, or gene amplification. As a result, the binding affinity of a drug to its molecular target is reduced, rendering the therapy less effective. A classic example is the mutation in topoisomerase II, which decreases the sensitivity of cancer cells to etoposide and doxorubicin[42]. Similarly, mutations in the β-tubulin gene affect the binding of taxanes and vinca alkaloids, leading to microtubule destabilization and impaired drug efficacy. In targeted therapies, such as tyrosine kinase inhibitors (TKIs), mutations in the kinase domain (e.g., EGFR T790M or BCR-ABL T315I) result in resistance to first-generation drugs[43]. These mutations often arise under selective pressure from long-term therapy and are a hallmark of acquired resistance. Additionally, cancer cells may downregulate the expression of the target altogether or utilize redundant signaling pathways, thereby diminishing the drug's impact[43]. Addressing this mechanism requires either developing next-generation drugs that can bind to mutant forms of the target or employing combination strategies to block alternative survival routes. Personalized medicine approaches are critical to circumventing such resistance.

2.4 Enhanced DNA Repair: Cancer cells often develop chemoresistance by enhancing their DNA repair capacity to counteract the genotoxic effects of many chemotherapeutic agents. Drugs like alkylating agents, platinum compounds, and topoisomerase inhibitors function by inducing DNA damage that leads to cell death. However, when DNA repair mechanisms are upregulated, cancer cells can effectively correct these lesions, survive, and proliferate[44]. Several key pathways are involved in this process, including base excision repair (BER), homologous recombination (HR), nucleotide excision repair (NER), and non-homologous end joining (NHEJ). For instance, increased expression of BRCA1/2, RAD51, or PARP enzymes enhances the cell's ability to repair double-strand breaks via HR[45]. This is particularly problematic in cancers that are initially sensitive to DNA-damaging agents, such as ovarian and triple-negative breast cancers. Moreover, overactivation of ATM and ATR kinases in the DNA damage response cascade enables the coordination of repair and cell cycle checkpoint control. Therapeutic strategies such as PARP inhibitors aim to exploit deficiencies in repair mechanisms (e.g., synthetic lethality in BRCA-mutant tumors), but resistance can still develop through restoration of HR function[46]. A better understanding of the interplay between DNA repair and drug resistance is vital for refining current therapies and overcoming resistance.

2.5 Apoptotic Evasion: The ability of cancer cells to evade apoptosis is a defining hallmark of tumor progression and a major contributor to chemoresistance. Apoptosis, or programmed cell death, is a tightly regulated process triggered by both intrinsic (mitochondrial) and extrinsic (death receptor) pathways[47]. Many chemotherapeutic agents rely on the activation of apoptosis to eliminate cancer cells. However, tumors can acquire mutations or dysregulate key proteins involved in this process. For instance, overexpression of anti-apoptotic proteins such as Bcl-2, Bcl-xL, and Mcl-1 inhibits mitochondrial outer membrane permeabilization, preventing cytochrome c release and caspase activation[48]. Concurrently, downregulation or mutation of pro-apoptotic factors like p53, Bax, or caspase-3 further impairs apoptotic signaling. p53, a crucial tumor suppressor and regulator of the DNA damage response, is frequently mutated in cancers, thereby compromising cell cycle arrest and apoptotic initiation in response to therapy. Moreover, upregulation of survival pathways such as PI3K/Akt and NF-κB enhances resistance to apoptotic stimuli[49, 50]. These alterations allow cancer cells to persist despite substantial genomic damage or stress. Therapeutic approaches targeting apoptotic regulators, such as BH3 mimetics (e.g., venetoclax), are being developed to restore apoptosis and overcome resistance in certain malignancies[49].

2.6 Tumor Microenvironment (TME): The tumor microenvironment (TME) is a complex and dynamic network composed of cancer cells, stromal cells, immune cells, extracellular matrix (ECM), and various signaling molecules[51]. It plays a crucial role in modulating chemoresistance through both physical and biochemical means. Hypoxia, a common feature of rapidly growing tumors, promotes the stabilization of hypoxia-inducible factors (HIFs), which in turn upregulate genes involved in angiogenesis, drug efflux, and metabolic reprogramming. Acidic pH within the TME, resulting from lactic acid accumulation via anaerobic glycolysis, can reduce the efficacy of weakly basic chemotherapeutic drugs by altering their ionization and uptake[52]. Additionally, dense ECM components such as collagen and fibronectin act as physical barriers, limiting drug penetration and distribution within the tumor mass. Stromal cells, including cancer-associated fibroblasts (CAFs), secrete growth factors and cytokines that activate survival pathways in cancer cells, such as PI3K/Akt and STAT3[53]. Immune cells like tumor-associated macrophages (TAMs) can also contribute to resistance by releasing anti-inflammatory cytokines or promoting epithelial–mesenchymal transition (EMT),

enhancing invasiveness and stemness. Furthermore, the TME can induce autophagy as a stress response, allowing cancer cells to survive under therapeutic pressure. Targeting TME components is therefore essential to overcoming resistance and improving drug delivery[54].

3. Nanomedicine Strategies to Overcome Chemoresistance

3.1 Inhibition of Efflux Transporters: One major mechanism of chemoresistance in cancer is the overexpression of efflux transporters such as P-glycoprotein (P-gp), which actively pump drugs out of cancer cells[55]. Nanocarriers can be engineered to avoid recognition by these efflux proteins or to co-deliver chemotherapeutic drugs with efflux pump inhibitors like verapamil or tariquidar[25, 29]. This dual-delivery strategy improves intracellular drug retention and enhances cytotoxic efficacy. Moreover, encapsulating drugs in liposomes, micelles, or polymeric nanoparticles protects them from being ejected prematurely, thereby improving therapeutic outcomes. This approach increases the effective concentration of anticancer drugs within tumor cells, overcoming resistance.

3.2 Gene Silencing and RNAi Nanocarriers: RNA interference (RNAi)-based nanotherapeutics represent a promising strategy to reverse chemoresistance by silencing genes responsible for drug resistance[56, 57]. Nanocarriers can deliver small interfering RNAs (siRNAs) or microRNAs (miRNAs) that specifically target and suppress resistance-related genes such as MDR1, BCL2, or MDM2. Lipid-based, polymer-based, or dendrimer-based nanoparticles protect RNAi molecules from enzymatic degradation in circulation and ensure their uptake by tumor cells. Once internalized, these RNA molecules can knock down key resistance pathways, sensitize tumors to chemotherapy, and enhance apoptosis. This method offers high specificity, minimal off-target effects, and a novel route to overcome multidrug resistance in cancer therapy[58].

3.3 Stimuli-Responsive Nanocarriers: Stimuli-responsive nanocarriers are "smart" drug delivery systems designed to release their therapeutic payload only in the presence of specific tumor-associated stimuli, thereby improving targeting accuracy[24, 59, 60]. These nanocarriers can respond to environmental cues in the tumor microenvironment (TME), such as acidic pH, elevated glutathione levels, or specific enzymes like matrix metalloproteinases. Upon exposure to these stimuli, the nanocarrier undergoes structural changes, triggering site-specific drug release. This enhances drug accumulation in tumor cells while minimizing damage to healthy tissues. As a result, stimuli-responsive nanoparticles significantly improve the therapeutic index of anticancer agents and reduce systemic toxicity[61, 62].

3.4 Targeting DNA Repair and Apoptotic Pathways: Chemoresistant cancer cells often exhibit enhanced DNA repair capabilities and evasion of apoptosis[63]. Nanoparticles co-loaded with DNA-damaging agents (e.g., cisplatin) and DNA repair inhibitors (e.g., PARP inhibitors) can overwhelm the cancer cell's repair mechanisms, making them more susceptible to therapy[63]. Additionally, nanocarriers can deliver pro-apoptotic molecules such as BH3 mimetics that restore apoptotic signaling pathways, tipping the balance toward cell death. This dual-targeted approach not only increases chemotherapy efficacy but also reduces the likelihood of resistance development[63]. The precise delivery enabled by nanoparticles ensures these agents reach their intracellular targets with minimal off-target effects.

3.5 Modulation of Tumor Microenvironment: The tumor microenvironment (TME) contributes significantly to chemoresistance through abnormal vasculature, dense extracellular matrix (ECM), and immunosuppressive cell populations[10, 59, 64]. Nanomedicine offers tools to modulate the TME and enhance therapeutic response. For instance, nanoparticles can deliver agents that normalize blood vessels, improving drug perfusion and oxygenation. Enzyme-sensitive nanoparticles, such as those responsive to matrix metalloproteinases, can degrade the ECM, allowing deeper drug penetration[65]. Additionally, nanocarriers can deliver immunomodulatory agents that reprogram immune cells to mount anti-tumor responses. By remodeling the TME, these strategies improve drug accessibility and potency while mitigating the supportive conditions that facilitate tumor survival and resistance.

4. Clinical Translation and Emerging Therapies

Several nanomedicine formulations have reached clinical trials or gained regulatory approval, such as liposomal doxorubicin (Doxil) and albumin-bound paclitaxel (Abraxane). Newer formulations integrating gene therapy, immunomodulators, or CRISPR-Cas9 systems are under investigation[18, 60, 66]. Challenges in clinical translation include manufacturing scalability, batch reproducibility, long-term toxicity, and regulatory hurdles. Nonetheless, advances in biomaterials, artificial intelligence-guided design, and personalized nanomedicine are driving progress.[67]

5. Future Directions and Conclusion

The future of nanomedicine lies in multifunctional and patient-specific platforms capable of simultaneous diagnosis, therapy, and resistance monitoring. Combining nanotechnology with precision oncology, immunotherapy, and artificial intelligence will revolutionize the management of chemoresistant cancers. In conclusion, nanomedicine provides a powerful and versatile approach to overcoming chemoresistance through

targeted delivery, co-therapeutics, and modulation of resistance mechanisms. Continued research and interdisciplinary collaboration will be pivotal to translating these innovations from bench to bedside.

CONCLUSION

Nanomedicine holds transformative potential in overcoming chemoresistance, a significant obstacle in effective cancer therapy. Through precise drug delivery, targeted tumor accumulation, and the ability to co-deliver multiple agents, nanocarriers can bypass traditional resistance mechanisms such as drug efflux pumps, enhanced DNA repair, and anti-apoptotic signaling. Mechanistic insights into how nanoparticles interact with the tumor microenvironment, cellular uptake pathways, and intracellular trafficking have guided the rational design of nanotherapeutics with enhanced efficacy. Moreover, innovations such as stimulus-responsive nanocarriers, gene-silencing platforms (e.g., siRNA and miRNA delivery), and combination strategies integrating chemotherapy with immunotherapy, photothermal therapy, or photodynamic therapy provide multifaceted approaches to sensitize resistant tumors. Despite these promising advances, clinical translation remains a challenge due to issues related to nanocarrier toxicity, scalability, pharmacokinetics, and regulatory hurdles. Future research must focus on optimizing biocompatibility, enhancing tumor specificity, and conducting rigorous clinical trials to validate preclinical findings. Integrating nanotechnology with precision oncology, systems biology, and artificial intelligence may offer novel predictive tools and personalized treatment strategies. Ultimately, the continued evolution of nanomedicine offers a compelling opportunity to reshape the therapeutic landscape, improving outcomes for patients who face drug-resistant cancers and advancing the frontier of cancer care.

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