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RESEARCH PAPER

Advancements in Polymeric Nanocarriers: Cisplatin and siRNA-Based Strategies for Tumor Growth Suppression and Overcoming Resistance in Non-Small Cell Lung Cancer

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ABSTRACT

Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related deaths worldwide, with a high prevalence and poor prognosis due to inherent and acquired resistance mechanisms. Cisplatin remains one of the most commonly used chemotherapeutic agents for NSCLC, functioning primarily through DNA damage-induced apoptosis. However, the emergence of resistance pathways such as increased DNA repair, drug efflux mechanisms, and activation of survival signaling pathways significantly limits its long-term efficacy. To address this challenge, small interfering RNA (siRNA) therapy has gained attention as a targeted approach to silence key genes responsible for cisplatin resistance, enhancing the drug's cytotoxic effects. Despite its potential, efficient delivery of siRNA remains a major hurdle due to its instability, rapid enzymatic degradation, and low cellular uptake. Polymeric nanocarriers have emerged as promising vehicles for drug delivery, offering controlled release, enhanced cellular uptake, and improved bioavailability of both cisplatin and siRNA. Their ability to encapsulate and protect therapeutic agents enables synergistic effects in tumor suppression and resistance modulation. Various polymer-based delivery platforms, including poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG)-modified systems, and chitosan-based nanoparticles, have demonstrated improved treatment outcomes in preclinical studies. These nanocarriers not only facilitate targeted drug delivery but also enhance the therapeutic index by reducing systemic toxicity. This review provides a comprehensive analysis of the advancements in polymeric nanocarriers for co-delivery of cisplatin and siRNA in NSCLC treatment. It explores the molecular mechanisms of tumor growth and drug resistance, the design and functionalization of polymeric carriers, and their role in overcoming treatment limitations. By discussing preclinical and clinical findings, this work aims to highlight the potential of these strategies for improving patient outcomes and addressing key challenges in NSCLC therapy.

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INTRODUCTION

Lung cancer remains one of the most prevalent and deadly malignancies worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all cases [1]. Current therapeutic options include surgical resection, radiotherapy, chemotherapy, and targeted molecular therapies. Despite these approaches, prognosis remains poor due to late-stage diagnosis and the emergence of resistance mechanisms that diminish the efficacy of conventional treatments [2]. Chemotherapy, particularly platinum-based agents such as cisplatin, has been a cornerstone of NSCLC treatment due to its mechanism of inducing DNA damage and apoptosis in cancer cells [3]. However, its effectiveness is frequently undermined by intrinsic and acquired resistance mechanisms, including increased DNA repair capacity, drug efflux, and activation of anti-apoptotic pathways [4]. The introduction of RNA interference (RNAi) through siRNA-based therapies has opened new avenues for overcoming drug resistance in NSCLC. By specifically silencing genes responsible for tumor progression and chemoresistance, siRNA offers a highly targeted approach to cancer therapy [5]. Nevertheless, clinical translation of siRNA therapy faces considerable barriers, including instability in biological environments, limited cellular uptake, and challenges in systemic delivery [6]. Polymeric nanocarriers have emerged as a viable solution to address these limitations, enabling the co-delivery of cisplatin and siRNA in a controlled and efficient manner. These nanocarriers provide several advantages, including enhanced drug encapsulation, prolonged circulation time, improved tumor targeting, and reduced systemic toxicity[7]. Recent advancements in nanotechnology have enabled the design and functionalization of polymeric carriers with tailored properties to optimize drug delivery [8]. Polymeric nanoparticles such as PLGA, PEGylated systems, and chitosan-based carriers have shown promising results like increased therapeutic efficacy through enhanced drug stability and tumor penetration [9]. Moreover, functional modifications such as ligand-based targeting and charge-controlled release mechanisms have further improved their application in NSCLC therapy [10].

This review aims to explore the potential of polymeric nanocarriers in NSCLC treatment, focusing on their role in enhancing cisplatin efficacy and overcoming resistance mechanisms through siRNA co-delivery. By discussing key developments in drug delivery strategies, biomolecular interactions, and preclinical evaluations, we provide insights into their translational potential for improving patient outcomes in NSCLC therapy.

MECHANISMS OF TUMOR GROWTH AND DRUG RESISTANCE IN NSCLC

Molecular Pathways Involved in Tumor Progression

Non-small cell lung cancer (NSCLC) is characterized by a complex network of molecular pathways that regulate tumor progression, invasion, and metastasis. These pathways are responsible for uncontrolled cell proliferation, resistance to apoptosis, angiogenesis, and immune evasion, making NSCLC a difficult malignancy to treat effectively [11]. One of the most extensively studied pathways in NSCLC is the epidermal growth factor receptor (EGFR) signaling cascade. EGFR mutations occur in a significant proportion of NSCLC cases, leading to constitutive activation of downstream pathways, including the RAS-RAF-MEK-ERK signaling axis, which promotes cell cycle progression and uncontrolled growth [12]. Additionally, the PI3K-AKT pathway is frequently dysregulated in NSCLC, contributing to cell survival, anti-apoptotic signaling, and resistance to chemotherapy [13]. KRAS mutations, which are prevalent in NSCLC, result in the constitutive activation of downstream effectors, including the mitogen-activated protein kinase (MAPK) pathway, which drives tumorigenesis. These mutations are associated with poor prognosis and resistance to EGFR inhibitors, highlighting the need for alternative therapeutic strategies targeting KRAS-driven NSCLC [14]. The tumor microenvironment plays a critical role in facilitating NSCLC progression. Cancer-associated fibroblasts, immune cells, and extracellular matrix components interact with tumor cells to promote angiogenesis and immune evasion [15]. Hypoxia-inducible factor-1 (HIF-1) activation in hypoxic tumor regions enhances the expression of vascular endothelial growth factor (VEGF), stimulating blood vessel formation and supporting metastatic potential [16].

Additionally, alterations in the p53 tumor suppressor pathway are commonly observed in NSCLC, leading to a loss of apoptotic control and increased genomic instability [17]. The dysregulation of cell cycle regulators such as cyclin-dependent kinases (CDKs) further accelerates

tumor proliferation, reinforcing the aggressive nature of NSCLC [18].

Mechanisms of Cisplatin Resistance in NSCLC

Cisplatin remains a cornerstone chemotherapeutic agent for NSCLC, primarily acting by inducing DNA damage and triggering apoptosis in cancer cells. However, resistance to cisplatin develops through a series of intricate biological mechanisms that enable tumor cells to evade cytotoxic effects, leading to therapeutic failure and disease progression [3, 19]. One of the primary resistance mechanisms is the enhanced DNA repair capability of tumor cells. Cisplatin causes DNA cross-linking, which interferes with replication and transcription, ultimately leading to apoptosis [20]. However, NSCLC cells frequently upregulate nucleotide excision repair (NER) pathways, including the expression of excision repair cross-complementation group 1 (ERCC1), which efficiently removes cisplatin-induced DNA adducts, allowing tumor cells to survive [21]. Drug efflux is another major contributor to cisplatin resistance. Overexpression of ATP-binding cassette (ABC) transporters, such as multidrug resistance-associated protein 2 (MRP2) and breast cancer resistance protein (BCRP), facilitates the rapid removal of cisplatin from tumor cells, reducing intracellular drug accumulation and negating its cytotoxic effects [22]. Alterations in apoptotic signaling pathways further support cisplatin resistance. Upregulation of anti-apoptotic proteins, including members of the BCL-2 family, inhibits programmed cell death, enabling tumor survival despite DNA damage accumulation. In contrast, downregulation of pro-apoptotic factors such as Bax and caspase-3 diminishes the effectiveness of cisplatin-induced apoptosis [23]. Epigenetic modifications also play a pivotal role in NSCLC drug resistance. Aberrant DNA methylation, histone modifications, and microRNA dysregulation affect gene expression patterns that regulate cisplatin sensitivity. For example, hypermethylation of tumor suppressor genes and microRNA-induced repression of apoptotic genes contribute to enhanced resistance [24]. Additionally, the tumor microenvironment exerts protective effects against cisplatin cytotoxicity. Hypoxia-induced signaling enhances resistance via increased HIF-1α activity, leading to altered gene expression favoring cell survival. Moreover, cancer-associated fibroblasts secrete growth factors and cytokines that shield NSCLC cells from chemotherapy-induced apoptosis, further complicating treatment efficacy [25].

Role of siRNA in Modulating Resistance

RNA interference (RNAi) has emerged as a powerful strategy for addressing cisplatin resistance in NSCLC by selectively silencing genes involved in drug efflux, DNA repair, apoptosis regulation, and tumor progression [26]. Small interfering RNA (siRNA) molecules are designed to target specific messenger RNAs (mRNAs), leading to their degradation and preventing the translation of proteins associated with resistance pathways [27]. One of the key applications of siRNA therapy in NSCLC is the inhibition of DNA repair mechanisms. Targeting ERCC1 or XPA with siRNA can significantly reduce the tumor's ability to repair cisplatin-induced DNA damage, sensitizing cancer cells to treatment. This approach enhances DNA adduct accumulation, increasing the likelihood of apoptosis following cisplatin exposure [28].

siRNA-mediated silencing of drug efflux transporters represents another promising avenue for overcoming resistance. Downregulation of ABCG2, MRP2, and P-glycoprotein (P-gp) restores intracellular cisplatin levels, ensuring sustained cytotoxic effects. By preventing rapid drug clearance, siRNA therapy enhances the efficacy of platinum-based chemotherapy [29]. Apoptotic dysregulation can also be addressed through siRNA interventions. By suppressing anti-apoptotic factors such as BCL-2, survivin, and XIAP, siRNA therapy promotes programmed cell death, restoring the ability of NSCLC cells to undergo apoptosis following cisplatin treatment. Simultaneously, activation of pro-apoptotic genes such as Bax and caspase-9 further strengthens therapeutic responses [30]. Epigenetic modulation using siRNA provides another layer of resistance control. siRNA targeting histone-modifying enzymes or methylation regulators can restore tumor suppressor gene function, reversing cisplatin insensitivity. Additionally, siRNA-induced alterations in microRNA expression profiles can modulate pathways responsible for tumor progression and chemotherapy resistance [31]. Efficient delivery of siRNA remains a major challenge due to its susceptibility to enzymatic degradation and poor cellular uptake. Polymeric nanocarriers offer a viable solution by encapsulating siRNA, protecting it from degradation, and facilitating

targeted delivery to tumor sites. Functionalized nanocarriers enhance intracellular uptake and enable controlled release, maximizing therapeutic efficiency [32].

POLYMERIC NANOCARRIERS: DESIGN AND FUNCTIONALIZATION

Types of Polymeric Nanocarriers

Polymeric nanocarriers have gained significant attention in drug delivery due to their ability to encapsulate therapeutic agents, protect them from degradation, and provide controlled release [33]. Among the various polymer-based systems, poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG)-modified carriers, and chitosan-based nanoparticles are widely studied for their biocompatibility and functional advantages [34]. PLGA nanoparticles are extensively used due to their biodegradability and regulatory approval for pharmaceutical applications. PLGA undergoes hydrolysis in physiological conditions, breaking down into lactic acid and glycolic acid, which are naturally metabolized by the body [35]. This property makes PLGA an ideal carrier for sustained drug release, particularly in cancer therapy and vaccine delivery. Additionally, PLGA nanoparticles can be engineered with surface modifications to enhance targeting and cellular uptake [36]. The ability to control the degradation rate by adjusting the lactic-to-glycolic acid ratio allows for precise tuning of drug release profiles, making PLGA a versatile option for various therapeutic applications [37]. PEGylated nanocarriers incorporate polyethylene glycol chains onto their surface, improving circulation time and reducing immune recognition. PEGylation prevents opsonization and clearance by the mononuclear phagocyte system, allowing nanoparticles to remain in systemic circulation longer [38]. This modification is particularly beneficial for targeted drug delivery in cancer therapy, where prolonged circulation enhances tumor accumulation. PEGylated nanoparticles can also be functionalized with ligands or antibodies to improve specificity toward diseased tissues [38]. The hydrophilic nature of PEG provides a steric barrier that minimizes protein adsorption, further enhancing nanoparticle stability and reducing aggregation [39]. Chitosan-based nanoparticles offer mucoadhesive properties and enhanced cellular interaction, making them suitable for oral, nasal, and transdermal drug delivery [40]. Chitosan is a natural polysaccharide with biodegradable and antimicrobial properties, allowing it to serve as an effective carrier for gene therapy, vaccine delivery, and antimicrobial agents [41]. Additionally, chitosan nanoparticles can be modified with cationic or hydrophilic coatings to improve drug encapsulation and release profiles. The positive charge of chitosan facilitates interaction with negatively charged cell membranes, improving cellular uptake and bioavailability [42].

Surface Modifications for Enhanced Targeting

Surface modifications play a crucial role in optimizing polymeric nanocarriers for targeted drug delivery and improved therapeutic efficacy. Several strategies have been developed to enhance nanoparticle interactions with biological systems, ensuring precise drug localization and reduced off-target effects[43]. One of the most common surface modifications is PEGylation, which improves nanoparticle stability and prolongs circulation time. PEGylated nanocarriers evade immune detection, reducing clearance by macrophages and enhancing drug accumulation at target sites [44]. Additionally, PEGylation can be combined with ligand conjugation, allowing nanoparticles to selectively bind to cancer cells or diseased tissues [45]. Another effective strategy is pH-responsive surface modification, where nanoparticles are designed to release their payload in acidic tumor microenvironments. This approach utilizes pH-sensitive polymers that undergo structural changes in acidic conditions, triggering drug release specifically at tumor sites. Such modifications improve therapeutic efficacy while minimizing systemic toxicity [46]. Cell-penetrating peptides are also employed to enhance nanoparticle uptake by target cells. These peptides facilitate endosomal escape and intracellular drug delivery, ensuring efficient transport of therapeutic agents into the cytoplasm. This modification is particularly useful for siRNA and gene therapy applications, where intracellular delivery is critical for therapeutic success [47]. Additionally, targeting ligands such as antibodies, aptamers, and folic acid can be conjugated to nanoparticle surfaces to improve specificity. These ligands enable receptor-mediated endocytosis, ensuring selective drug uptake by diseased cells while minimizing interactions with healthy tissues [48].

Biocompatibility and Stability Considerations

Biocompatibility and stability are essential factors in the design of polymeric nanocarriers, ensuring safe and effective drug delivery. Several considerations must be addressed to optimize nanoparticle performance and minimize adverse effects [49].

Biocompatibility is influenced by polymer selection, surface charge, and degradation kinetics. PLGA, PEGylated, and chitosan-based nanoparticles are widely used due to their low toxicity and biodegradability. However, surface modifications such as cationic coatings can affect cellular interactions, necessitating careful optimization to prevent cytotoxicity [50]. Stability considerations include nanoparticle aggregation, drug leakage, and environmental sensitivity. PEGylation improves nanoparticle stability by reducing protein adsorption and preventing aggregation, ensuring prolonged circulation and enhanced drug delivery. Additionally, crosslinking strategies can be employed to stabilize polymeric matrices, preventing premature drug release [38]. Storage conditions also play a critical role in nanoparticle stability. Factors such as temperature, pH, and ionic strength can impact nanoparticle integrity, requiring optimized formulations for long-term storage and clinical applications [51].

CISPLATIN DELIVERY VIA POLYMERIC NANOCARRIERS

Encapsulation Strategies for Cisplatin

Cisplatin is a platinum-based chemotherapeutic agent widely used for treating various cancers, including non-small cell lung cancer. Despite its effectiveness, its clinical application is often hindered by poor aqueous solubility, rapid systemic clearance, severe nephrotoxicity, and the development of drug resistance [52]. To address these limitations, polymeric nanocarriers have been developed as an advanced drug delivery system, offering improved encapsulation, controlled release, and enhanced tumor targeting [33]. Encapsulation of cisplatin within polymeric nanoparticles can be achieved through various techniques, including nanoprecipitation, emulsification-solvent evaporation, ionic gelation, and electrostatic complexation [53]. These methods allow for precise control over nanoparticle size, drug loading efficiency, and release kinetics, ensuring optimal therapeutic performance [54]. One of the most widely studied polymeric nanocarriers for cisplatin delivery is poly(lactic-co-glycolic acid) (PLGA). PLGA nanoparticles provide a biodegradable and biocompatible matrix for drug encapsulation, allowing for sustained cisplatin release while minimizing systemic toxicity [55]. The degradation rate of PLGA can be tailored by adjusting the lactic-to-glycolic acid ratio, enabling precise control over drug release kinetics [56]. Additionally, PLGA nanoparticles can be surface-modified with polyethylene glycol (PEG) to enhance circulation time and reduce immune recognition, further improving drug accumulation at tumor sites [57]. Another promising strategy involves the use of amphiphilic block copolymers, which self-assemble into micelles or vesicles that encapsulate cisplatin within their hydrophobic core. These nanocarriers enhance drug solubility and improve circulation time, allowing for prolonged drug exposure at tumor sites [58]. Block copolymers such as poly(ethylene glycol)-poly(caprolactone) (PEG-PCL) and poly(ethylene glycol)-poly(lactic acid) (PEG-PLA) have demonstrated significant potential in improving cisplatin delivery. These micellar systems provide a stable drug reservoir, preventing premature drug release and ensuring controlled cisplatin release in response to tumor-specific stimuli [59]. Lipid-polymer hybrid nanoparticles have also been developed to improve cisplatin encapsulation efficiency and stability. These systems combine the advantages of polymeric nanoparticles with lipid-based carriers, resulting in enhanced drug retention and controlled release properties [60]. Lipid-polymer hybrid nanoparticles typically consist of a polymeric core encapsulating cisplatin, surrounded by a lipid bilayer that enhances biocompatibility and cellular uptake. This hybrid approach improves drug stability, reduces premature degradation, and facilitates efficient tumor penetration [61]. Controlled release mechanisms are essential for optimizing cisplatin delivery, ensuring sustained drug exposure while minimizing toxicity. Polymeric nanocarriers can be engineered to release cisplatin in response to specific physiological conditions, such as pH changes, enzymatic activity, or redox potential [62]. Some studies showed pH-sensitive drug release, where nanoparticles are designed to degrade in acidic tumor microenvironments. Tumor tissues typically exhibit a lower pH than normal tissues due to increased glycolysis and lactate production [63]. By incorporating pH-sensitive polymers

such as poly(acrylic acid) or methacrylate-based copolymers into nanocarrier formulations, cisplatin release can be triggered selectively in acidic regions, promoting greater tumor accumulation and reducing systemic exposure [64]. Redox-responsive nanocarriers represent another promising strategy for controlled cisplatin delivery. The intracellular environment of cancer cells is characterized by elevated levels of glutathione, a reducing agent that plays a key role in maintaining redox balance [65]. Cisplatin-loaded nanoparticles with disulfide linkages are engineered to undergo cleavage in high-glutathione conditions, leading to selective drug release inside cancer cells [66]. Enzyme-responsive nanocarriers have also been explored for cisplatin delivery, leveraging the activity of tumor-associated enzymes such as matrix metalloproteinases and cathepsins. These enzymes play a crucial role in tumor invasion and metastasis, making them ideal triggers for drug release [67]. Enzyme-cleavable peptide linkers are often incorporated into the nanoparticle matrix, ensuring that drug activation occurs specifically within tumor tissues where these enzymes are highly expressed [68]. By integrating protease-sensitive components into polymeric carriers, cisplatin release can be tailored to coincide with areas of high enzymatic activity, thereby maximizing therapeutic efficacy while minimizing off-target effects [69]. In addition to biological triggers, external stimuli-responsive nanocarriers provide another layer of control for cisplatin delivery. Ultrasound-responsive carriers have been engineered using gas-generating polymers or microbubbles that respond to focused ultrasound waves, causing a disruption in the nanoparticle structure and facilitating controlled drug release [70]. Magnetic field-responsive nanocarriers utilize iron oxide-based nanoparticles that release cisplatin upon exposure to alternating magnetic fields, enhancing drug accumulation within specific tumor regions. These externally controlled systems enable real-time modulation of cisplatin release, offering an adaptable therapeutic strategy for precision oncology [71].

Controlled Release Mechanisms

Controlled release mechanisms are fundamental in optimizing cisplatin delivery, ensuring prolonged drug exposure while minimizing systemic toxicity. Polymeric nanocarriers have been developed with sophisticated structural and chemical designs to achieve precise cisplatin release based on specific physiological stimuli [72]. These stimuli-responsive mechanisms allow for more efficient drug targeting, enhancing therapeutic effectiveness while reducing undesirable effects on healthy tissues [73]. One of the most approaches is pH-sensitive drug release, in which nanoparticles are designed to degrade in acidic tumor microenvironments. Tumor tissues typically exhibit a lower pH than normal tissues due to increased glycolysis and lactate production [74]. By incorporating pH-sensitive polymers such as poly(acrylic acid) or methacrylate-based copolymers into nanocarrier formulations, cisplatin release can be triggered selectively in acidic regions, promoting greater tumor accumulation and reducing systemic exposure. This approach is particularly valuable for enhancing the efficacy of cisplatin while limiting nephrotoxicity and gastrointestinal disturbances associated with conventional formulations [64]. Redox-responsive nanocarriers represent another promising strategy for controlled cisplatin delivery. The intracellular environment of cancer cells is characterized by elevated levels of glutathione, a reducing agent that plays a key role in maintaining redox balance [75]. Cisplatin-loaded nanoparticles with disulfide linkages are engineered to undergo cleavage in high-glutathione conditions, leading to selective drug release inside cancer cells. This approach ensures enhanced cytotoxicity at tumor sites while preventing premature drug release during systemic circulation. Additionally, redox-sensitive nanocarriers can be designed with thiolated polymers or conjugated cysteine residues to further improve drug retention and targeted release within the tumor microenvironment[66]. Enzyme-responsive nanocarriers have also been explored for cisplatin delivery, leveraging the activity of tumor-associated enzymes such as matrix metalloproteinases and cathepsins [66]. These enzymes play a crucial role in tumor invasion and metastasis, making them ideal triggers for drug release. Enzyme-cleavable peptide linkers are often incorporated into the nanoparticle matrix, ensuring that drug activation occurs specifically within tumor tissues where these enzymes are highly expressed [68]. By integrating protease-sensitive components into polymeric carriers, cisplatin release can be tailored to coincide with areas of high enzymatic activity, thereby maximizing therapeutic efficacy while minimizing off-target effects [69]. In addition to biological

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siRNA-BASED APPROACHES FOR OVERCOMING RESISTANCE

Mechanism of RNA Interference in Cancer Therapy

RNA interference is a highly specific gene-silencing mechanism that regulates gene expression at the post-transcriptional level, allowing for precise suppression of target messenger RNA molecules [76]. This process is mediated by small interfering RNA molecules, which bind to complementary sequences on the mRNA, directing its degradation and preventing protein synthesis. The ability to selectively inhibit gene expression has positioned RNA interference as a transformative tool in cancer therapy, particularly for addressing mechanisms of drug resistance [77]. Cancer cells frequently develop resistance to chemotherapy through the upregulation of genes involved in survival pathways, DNA repair, and drug efflux [78]. These genetic modifications enable tumors to withstand chemotherapy-induced damage, limiting the therapeutic efficacy of conventional drugs. By utilizing siRNA, these resistance-related genes can be silenced, thereby sensitizing cancer cells to treatment [79]. Genes associated with enhanced DNA repair mechanisms, such as excision repair cross-complementation group 1 and X-ray repair cross-complementing protein 1, can be suppressed, impairing the tumor's ability to recover from chemotherapy-induced damage and increasing its vulnerability to cytotoxic agents [80]. Beyond targeting DNA repair pathways, siRNA can also be employed to downregulate genes responsible for drug efflux. Many resistant tumors express ATP-binding cassette transporters, such as ABCG2 and multidrug resistance protein 1, which facilitate the removal of therapeutic agents from the intracellular space, thereby reducing drug accumulation and efficacy. By inhibiting the expression of these transport proteins, siRNA therapy ensures higher intracellular concentrations of chemotherapeutic agents, enhancing therapeutic response [81]. Additionally, siRNA can modulate apoptotic signaling pathways, ensuring that tumor cells retain their susceptibility to programmed cell death when exposed to cytotoxic drugs [82]. Suppression of anti-apoptotic proteins such as B-cell lymphoma 2 and survivin restores apoptotic sensitivity, allowing chemotherapy-induced DNA damage to effectively trigger cell death rather than adaptation and resistance [83]. Despite the promising potential of siRNA-based treatments, several challenges hinder their clinical translation. These challenges include limited stability in biological fluids, rapid enzymatic degradation, and inefficient uptake by target cells [84]. Naked siRNA molecules are highly susceptible to degradation by nucleases, leading to reduced therapeutic efficacy [85]. Polymeric nanocarriers, such as poly(lactic-co-glycolic acid) nanoparticles, provide a biodegradable and biocompatible platform for siRNA delivery. These carriers can be engineered with surface modifications to improve cellular uptake and enhance tumor targeting. Lipid-based nanoparticles, including liposomes and solid lipid nanoparticles, offer additional advantages, such as improved circulation time and reduced immune recognition [86]. Inorganic nanoparticles, such as gold and silica-based carriers, provide structural stability and tunable surface properties, allowing for precise control over siRNA release kinetics [87]. Functionalized nanocarriers incorporating tumor-specific ligands, such as folic acid or transferrin, improve selectivity and minimize off-target effects [88]. Additionally, stimuli-responsive nanocarriers, designed to release their payload in response to pH changes, enzymatic activity, or redox potential, enable precise drug activation within the tumor microenvironment [70].

Synergistic Effects with Cisplatin

The synergistic effects of siRNA and cisplatin in cancer therapy stem from their complementary mechanisms of action, which collectively enhance cytotoxic efficacy while mitigating resistance pathways [89]. Cisplatin primarily functions by forming DNA adducts that disrupt replication and transcription, ultimately triggering apoptosis [90].

However, tumor cells often develop resistance through enhanced DNA repair mechanisms, increased drug efflux, and activation of survival pathways. The incorporation of siRNA therapy into cisplatin-based treatment regimens offers a multifaceted approach to overcoming these resistance mechanisms, thereby improving therapeutic outcomes [20]. One of the most significant advantages of siRNA therapy is its ability to selectively silence genes involved in cisplatin resistance. DNA repair proteins such as excision repair cross-complementation group 1 (ERCC1) and X-ray repair cross-complementing protein 1 (XRCC1) play crucial roles in repairing cisplatin-induced DNA damage, allowing tumor cells to evade apoptosis [26]. By employing siRNA to downregulate these repair proteins, the persistence of DNA lesions increases, leading to enhanced cytotoxicity and reduced tumor survival [91]. Additionally, siRNA targeting ATP-binding cassette (ABC) transporters, such as ABCG2 and multidrug resistance protein 1 (MDR1), can inhibit drug efflux, ensuring higher intracellular cisplatin concentrations and prolonged exposure to its cytotoxic effects [92]. Beyond modulating DNA repair and drug efflux, siRNA therapy can also influence apoptotic signaling pathways. Tumor cells frequently upregulate anti-apoptotic proteins such as B-cell lymphoma 2 (BCL-2) and survivin, which inhibit programmed cell death and contribute to chemotherapy resistance [93]. siRNA-mediated suppression of these proteins restores apoptotic sensitivity, allowing cisplatin-induced DNA damage to effectively trigger cell death. Furthermore, siRNA can be designed to target oncogenic signaling pathways, such as phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK), which promote tumor survival and proliferation [94]. The development of hybrid nanocarrier systems capable of co-delivering siRNA and cisplatin has further optimized this therapeutic strategy. Polymeric nanoparticles, lipid-based carriers, and inorganic nanostructures have been engineered to encapsulate both agents, ensuring synchronized delivery and controlled release [95]. These nanocarriers protect siRNA from enzymatic degradation, enhance cellular uptake, and facilitate targeted delivery to tumor tissues. Functionalized nanoparticles incorporating tumor-specific ligands, such as folic acid or transferrin, improve selectivity and minimize off-target effects [96]. Additionally, stimuli-responsive nanocarriers, designed to release their payload in response to pH changes, enzymatic activity, or redox potential, enable precise drug activation within the tumor microenvironment [70].

PRECLINICAL AND CLINICAL STUDIES

Ana Vanessa Nascimento et al [97], explored a combination therapy for lung cancer using epidermal growth factor receptor (EGFR)-targeted chitosan (CS) nanoparticles loaded with Mad2 siRNA alongside cisplatin. The Mad2 siRNA silences a crucial mitotic checkpoint gene to induce cell death. When tested in both cisplatin-sensitive and resistant lung cancer models, the combination therapy significantly improved tumor inhibition, with particularly strong effects in drug-resistant tumors. A major advantage of this strategy was the substantial reduction in cisplatin dosage required, leading to minimal toxicity. Key indicators—such as body weight, biochemical markers for liver and kidney function, and histopathological assessments—confirmed the safety of the approach. This research highlights the potential of siRNA-based nanocarrier systems to enhance chemotherapy efficacy while reducing adverse effects, offering a promising method for treating drug-resistant cancers.

Chunshan Shi et al [98], examined cisplatin-loaded poly(l-glutamic acid)-g-methoxy poly(ethylene glycol 5K) nanoparticles (CDDP-NPs) for treating non-small cell lung carcinoma (NSCLC). The nanoparticles were found to be biodegradable, with their size and degradation rate influenced by pH and temperature. Additionally, CDDP-NPs exhibited cisplatin-like biological activity, including their ability to bind to nucleotides. Compared to free cisplatin, CDDP-NPs showed lower renal platinum accumulation, reducing toxicity. In vivo experiments using a Lewis lung carcinoma (LLC) model demonstrated that CDDP-NPs effectively suppressed tumor growth. Mice treated with CDDP-NPs experienced significantly longer survival rates, with a median of 51 days compared to 18 days for those receiving free cisplatin, indicating improved therapeutic efficacy and reduced systemic toxicity. These findings suggest that CDDP-NPs could serve as a promising lower-toxicity alternative for NSCLC treatment.

Vivek Patel et al [99], Hybrid nanocarriers composed of lipids and PEG-PLA copolymer were prepared for co-delivery of cisplatin caprylate

and ABCC3-siRNA. PEGylation was performed using the post-insertion technique. The optimized formulation showed 71.9 ± 2.2% and 95.83 ± 0.39% entrapment efficiency for cisplatin caprylate and siRNA, respectively. The hydrodynamic diameter was 153.2 ± 1.76 nm and the zeta potential was +25.39 ± 0.49 mV. Cryo-TEM analysis confirmed a lipid bilayer surrounding the polymeric core. Cellular uptake was improved. Cytotoxic potential was enhanced in A549 cells compared to drug solution and drug-loaded nanocarriers. Cell cycle analysis showed increased G2-M phase arrest compared to drug-loaded nanocarriers. ABCC3 mRNA silencing improved efficacy. Tumor regression was observed in an A549 xenograft model in BALB/c nude mice. The formulation increased half-life and reduced drug resistance, showing potential for cisplatin-based NSCLC treatment.

Shanthi Ganesh et al [100], demonstrated Tandem delivery of siRNAs targeting anti-apoptotic genes in cisplatin-resistant tumors followed by treatment with cisplatin-loaded CD44-targeted hyaluronic acid nanoparticles induced a synergistic antitumor response in CD44-expressing cisplatin-resistant tumors. Near-infrared dye-loaded hyaluronic acid nanoparticles were used to image nanoparticle distribution after intravenous injection into mice bearing human lung tumors, both sensitive and resistant to cisplatin. siRNA duplexes and cisplatin dose distribution were quantified in tissues and organs using quantitative PCR and inductively coupled plasma-mass spectrometry after intravenous injection of payload-loaded nanoparticles. The distribution pattern of siRNA and cisplatin correlated with tumor targeting, demonstrating improved efficacy with combination treatments.

CONCLUSION AND FUTURE PERSPECTIVES

Polymeric nanocarriers have emerged as a transformative strategy for enhancing cisplatin delivery and overcoming drug resistance in non-small cell lung cancer. By leveraging nanotechnology, these systems offer improved encapsulation, targeted release, and synergistic effects when combined with siRNA therapy. Controlled release mechanisms, including pH-sensitive, redox-responsive, and enzyme-triggered approaches, have optimized cisplatin distribution, minimizing systemic toxicity while maximizing therapeutic efficacy. Additionally, the integration of siRNA allows for precise modulation of resistance pathways, reducing drug efflux and inhibiting survival mechanisms within tumor cells. The co-delivery of cisplatin and siRNA through advanced nanocarrier platforms holds great promise for improving patient outcomes and addressing the long-standing challenges associated with chemotherapy resistance. While significant progress has been made in preclinical studies, further research is required to refine nanocarrier formulations, enhance targeting efficiency, and ensure successful clinical translation.

Future perspectives in polymeric nanocarrier research focus on refining drug delivery systems to improve therapeutic precision, efficacy, and safety. Advancements in multi-functional nanoparticles that integrate multiple stimuli-responsive features, such as dual pH and redox sensitivity, are expected to enhance selective drug release at tumor sites, reducing systemic toxicity. Hybrid nanocarrier platforms that combine polymeric, lipid-based, and inorganic nanoparticles may offer improved drug stability, prolonged circulation, and better tumor penetration.

Personalized nanomedicine is another promising area, where drug-loaded nanocarriers are tailored to individual tumor profiles based on patient-specific biomarkers. With artificial intelligence-driven computational modeling, nanoparticle designs can be optimized for targeted delivery, ensuring maximum therapeutic benefits while minimizing adverse effects. The development of customizable drug formulations may help address variability in patient responses, allowing for more precise cancer treatment strategies. Further work is needed to overcome challenges in clinical translation and regulatory approval. Large-scale production of polymeric nanocarriers with consistent physicochemical properties and batch reproducibility remains a critical hurdle. Ensuring biocompatibility and minimizing immunogenic responses are key aspects that must be addressed before regulatory bodies approve nanocarrier-based treatments for widespread clinical use. Ongoing efforts in large-scale clinical trials will be essential to validate their safety and efficacy in diverse patient populations.

Polymeric nanocarriers also hold potential beyond cisplatin and siRNA therapy. Their applications may extend to gene editing technologies, immunotherapy enhancements, and multi-drug combination strategies for cancer

treatment. Emerging approaches incorporating CRISPR-based therapeutics and immune checkpoint modulators with nanoparticle carriers may pave the way for next-generation oncological treatments.

With continuous improvements in material engineering, nanoparticle functionalization, and tumor-targeting strategies, polymeric nanocarriers have the potential to revolutionize cancer therapy by providing safer, more efficient, and personalized treatments. Continued interdisciplinary research, combining expertise in nanotechnology, molecular biology, and pharmacology, will be crucial for realizing their full clinical potential.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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