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RESEARCH PAPER

Dual-Ligand Liposomes Nano carrier with Cisplatin and Anti-PD-L1 siRNA in Head and Neck Squamous Cell Carcinoma: A Review

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ABSTRACT

Head and neck squamous cell carcinoma (HNSCC) remains a therapeutic challenge due to its aggressive nature, immunosuppressive tumor microenvironment, and resistance to conventional therapies. Immune checkpoint modulation, particularly targeting the PD-1/PD-L1 axis, has shown promise but is limited by systemic toxicity and insufficient tumor-specific delivery. Combining chemotherapy with immune checkpoint blockade offers a synergistic strategy to enhance antitumor efficacy while mitigating immune evasion. This review explores the novel use of dual-ligand liposomes for the co-delivery of cisplatin, a platinum-based chemotherapeutic agent, and anti-PD-L1 siRNA to simultaneously induce tumor cell death and reverse PD-L1-mediated immunosuppression. By integrating two targeting ligands, these nanocarriers improve tumor specificity, reduce off-target effects, and enhance drug accumulation in HNSCC tissues. Preclinical studies demonstrate that this approach potentiates cisplatin's cytotoxic effects while silencing PD-L1 to activate cytotoxic T lymphocytes, fostering a durable antitumor immune response. The dual-ligand design addresses key limitations of single-ligand systems, offering a platform for precise, combinatorial therapy.

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INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer globally, with over 890,000 new cases annually [1]. It arises from mucosal epithelia in the oral cavity, pharynx, and larynx, often linked to tobacco use, alcohol consumption, and human papillomavirus (HPV) infection [2]. Despite advances in surgery, radiotherapy, and chemotherapy, the 5-year survival rate remains below 65% due to late diagnosis, metastasis, and recurrence [3]. New therapies for HNSCC are limited by systemic toxicity, chemoresistance, and an immunosuppressive tumor microenvironment (TME) [4]. Cisplatin, a cornerstone of HNSCC chemotherapy, often fails in advanced cases due to dose-limiting nephrotoxicity, neurotoxicity, and acquired resistance [4]. Additionally, tumor cells evade immune surveillance by upregulating PD-L1, which binds PD-1 on T cells to inhibit their activity [5]. Monotherapies targeting PD-1/PD-L1 achieve only modest response rates (15–20%), underscoring the need for combinatorial strategies [6]. Immune checkpoint inhibitors (ICIs) have revolutionized oncology, but their efficacy in HNSCC is hindered by poor TME penetration and adaptive resistance [7]. Silencing PD-L1 via siRNA offers a gene-editing approach to block immune evasion at its source, while cisplatin promotes immunogenic cell death (ICD), releasing tumor antigens that prime T-cell responses [8]. Combining these agents could synergistically enhance antitumor immunity and cytotoxicity. Co-delivering these agents ensures spatial-temporal coordination, maximizing therapeutic synergy while minimizing systemic immunosuppression [9].

Nanocarriers, particularly liposomes, improve drug solubility, prolong circulation, and enhance tumor targeting [10]. Dual-ligand liposomes functionalized with two distinct targeting moieties (e.g., folate and transferrin receptors) exploit overexpression of multiple receptors on HNSCC cells, enabling precise delivery to both tumor and immune cells. This design overcomes the heterogeneity of HNSCC and improves penetration into the dense TME [11].

The novelty of this approach lies in the integration of dual-ligand liposomes for simultaneous delivery of cisplatin and anti-PD-L1 siRNA. This review aims to evaluate the mechanistic basis, preclinical efficacy, and translational potential of this combinatorial nanotherapy, offering insights into its role in redefining immune checkpoint modulation for HNSCC treatment.

DUAL-LIGAND LIPOSOME DESIGN AND FORMULATION

Liposome Engineering for Dual-Targeting

Dual-ligand liposomes represent an advanced nanoscale drug delivery system designed to facilitate the co-administration of cisplatin and anti-PD-L1 siRNA. This formulation aims to enhance tumor-specific targeting, improve drug stability, and increase therapeutic efficacy, addressing challenges associated with tumor heterogeneity and immunosuppressive tumor microenvironments[12]. Cisplatin exerts cytotoxic effects by inducing DNA crosslinking and promoting immunogenic cell death, whereas anti-PD-L1 siRNA modulates immune responses by downregulating PD-L1 expression, thereby restoring T-cell function. The simultaneous delivery of these therapeutic agents is intended to optimize antitumor immune responses and inhibit mechanisms of immune evasion [13]. Traditional liposomal formulations primarily rely on passive accumulation; however, variability in tumor characteristics in head and neck squamous cell carcinoma can limit treatment efficacy [14]. The dual-ligand approach incorporates two receptor-targeting moieties, increasing binding affinity for both tumor cells and immune cells, thereby improving therapeutic delivery precision [15]. In head and neck squamous cell carcinoma, folate receptors and transferrin receptors are frequently overexpressed, facilitating selective tumor uptake [16]. Folate functions as an essential cofactor in DNA synthesis, with cancer cells exhibiting increased folate uptake due to heightened metabolic activity [17]. Similarly, transferrin plays a crucial role in iron homeostasis and is highly expressed in proliferative tumor cells, making it a viable targeting ligand [18]. The combination of folate and transferrin ligands in the dual-functionalized liposomal system ensures precise tumor accumulation, optimizing drug delivery efficiency [19]. Achieving effective drug penetration within the tumor microenvironment is critical for PD-L1 silencing and immune modulation [20].

siRNA Loading: Challenges and Solutions

The delivery of anti-PD-L1 siRNA presents several inherent challenges, primarily related to

its stability, cellular uptake, and susceptibility to nucleic acid degradation. Free siRNA molecules are highly vulnerable to enzymatic degradation by nucleases in circulation, resulting in a short half-life and limited therapeutic efficacy [21]. Additionally, the negative charge and hydrophilic nature of siRNA molecules hinder their ability to traverse lipid membranes, leading to poor intracellular penetration and inefficient gene silencing [22]. Overcoming these obstacles necessitates the development of optimized delivery systems that enhance siRNA stability, facilitate cellular entry, and ensure effective gene silencing without premature degradation. Several key challenges must be addressed to achieve successful siRNA delivery. One major limitation is rapid clearance from circulation, which significantly reduces bioavailability and necessitates stabilization strategies to extend siRNA half-life [23]. Low transfection efficiency further complicates therapeutic application, as siRNA must enter tumor cells efficiently and suppress PD-L1 expression without being neutralized prior to intracellular processing [24]. Another critical barrier is the endosomal escape limitation, wherein siRNA molecules are internalized via endocytosis but frequently undergo degradation within lysosomal compartments before reaching the cytoplasm, thereby reducing their functional availability for gene silencing [25]. To improve the stability and delivery efficiency of siRNA therapeutics, several formulation strategies have been explored. Cationic liposomes serve as an effective delivery platform by incorporating positively charged lipids that interact electrostatically with negatively charged siRNA molecules [26]. This electrostatic association enhances siRNA encapsulation, improves retention within lipid-based carriers, and facilitates cellular uptake [27]. Surface modifications such as polyethylene glycol functionalization further contribute to siRNA stabilization by shielding the therapeutic cargo from enzymatic degradation and immune recognition, thereby prolonging systemic circulation and enhancing biodistribution [23]. Additionally, endosomal escape strategies are critical for maximizing siRNA bioavailability within the cytoplasm [28]. Lipid-based carriers often integrate pH-sensitive compounds such as histidine-modified lipids, which induce endosomal membrane destabilization in response to acidic intracellular environments, facilitating the release of siRNA into the cytoplasm and ensuring effective gene silencing [29]. These optimization strategies collectively enhance the efficacy of PD-L1 suppression, thereby potentiating the immunomodulatory effects required for antitumor activity [30]. When combined with cisplatin-induced immunogenic cell death, siRNA-mediated PD-L1 downregulation contributes to sustained immune activation and improved therapeutic outcomes in head and neck squamous cell carcinoma [31].

Ligand Selection for Tumor-Specific Targeting

The selection of ligands for tumor-specific targeting is a critical factor in optimizing drug delivery, ensuring precise accumulation within tumor cells and immune compartments. While passive targeting strategies rely on the enhanced permeability and retention effect, active targeting mechanisms leverage ligand-receptor interactions to achieve selective drug localization [32]. By incorporating ligands that are overexpressed on malignant cells, it is possible to enhance therapeutic specificity while minimizing off-target effects. The strategic selection of ligands is particularly relevant in the context of head and neck squamous cell carcinoma, where tumor heterogeneity and an immunosuppressive microenvironment pose significant challenges to conventional drug delivery approaches [33]. Among the various targeting ligands investigated, folate has emerged as a highly effective molecule for tumor-specific drug accumulation. Folate receptors are frequently overexpressed in head and neck squamous cell carcinoma, facilitating ligand-mediated endocytosis and enhancing the intracellular delivery of therapeutic agents [34]. The high-affinity interaction between folate and its receptor allows selective uptake, reducing systemic exposure and minimizing off-target effects. This ligand is particularly advantageous in circumventing normal tissue accumulation, thereby improving the therapeutic index of liposomal formulations [35]. Transferrin represents another widely utilized ligand for active targeting. The transferrin receptor is highly expressed in proliferative tumor cells, playing a pivotal role in iron homeostasis and cellular metabolism [36]. The overexpression of transferrin receptors in malignant tissues makes transferrin an ideal targeting moiety for liposomal drug delivery systems. By facilitating receptor-mediated endocytosis, transferrin improves drug uptake efficiency and enhances tumor-specific

accumulation. This ligand is especially beneficial for nanoparticle-mediated cisplatin delivery, as iron metabolism influences tumor progression and therapeutic sensitivity [37]. Epidermal growth factor receptor inhibitors offer a targeted approach for addressing tumors with high EGFR expression. Certain head and neck squamous cell carcinoma subtypes exhibit elevated EGFR levels, which contribute to malignant progression and therapeutic resistance [38]. Ligands directed towards EGFR facilitate selective drug delivery, allowing liposomal formulations to preferentially bind to cancer cells exhibiting EGFR amplification. Targeting this receptor enhances intracellular drug retention and reinforces treatment efficacy, particularly in combination with immune-modulatory agents [39]. CD44-targeting moieties provide an additional avenue for improving tumor penetration and drug delivery specificity. CD44, a cell surface glycoprotein associated with tumor invasion and stemness, is frequently upregulated in head and neck squamous cell carcinoma [40]. The utilization of CD44-targeting ligands enables deeper tumor microenvironment penetration, improving intracellular drug bioavailability and reducing tumor recurrence risks [41]. An important consideration in ligand selection is the optimization of ligand density to prevent excessive binding affinity that may trigger rapid clearance mechanisms [42]. Overexpression of targeting moieties can lead to accelerated systemic elimination via mononuclear phagocytic system recognition, thereby reducing drug accumulation at the tumor site. Balancing ligand affinity is essential to ensure sufficient receptor-mediated uptake while avoiding premature degradation [43].

MECHANISMS OF ACTION

Cisplatin Encapsulation: Methods and Stability

Cisplatin is a platinum-based chemotherapeutic agent widely utilized in oncology due to its ability to induce DNA crosslinking, thereby disrupting tumor cell replication and promoting immunogenic cell death [44]. This mechanism of action renders cisplatin highly effective in treating various malignancies; however, its clinical utility is often constrained by dose-dependent toxicity and the emergence of drug resistance. These limitations necessitate the development of advanced drug delivery systems that can enhance cisplatin's therapeutic index while minimizing adverse effects [45]. Among the various strategies investigated, liposomal encapsulation has demonstrated considerable potential in improving cisplatin delivery by providing controlled release kinetics, reducing systemic toxicity, and increasing tumor-specific accumulation [46]. Liposomes, which are phospholipid-based vesicular systems, serve as biocompatible carriers that can encapsulate cisplatin within their aqueous compartments. Their structural versatility allows for modifications that enhance drug loading efficiency, stability, and bioavailability, ensuring optimal therapeutic efficacy upon administration [47]. Several techniques have been employed to encapsulate cisplatin within liposomes efficiently. The hydration and solvent evaporation method, a widely used approach, facilitates liposome formation while enabling cisplatin incorporation within the aqueous phase. This technique ensures adequate drug encapsulation while maintaining the physicochemical stability of the liposomal formulation [48]. Remote loading using pH gradients has also been extensively explored, where cisplatin is actively loaded into liposomes by exploiting pH differences. This method enhances drug retention and stability, preventing premature release during circulation [49]. In addition, modified lipid-polymer hybrids integrate polymeric stabilizers that improve cisplatin retention within liposomes, effectively mitigating the risk of premature leakage while preserving the drug's bioavailability [50]. Beyond enhancing drug stability and bioavailability, liposomal cisplatin formulations have demonstrated significant potential in mitigating cisplatin-induced toxicity. By modulating pharmacokinetics and biodistribution, liposome-mediated delivery achieves targeted tumor accumulation while preserving cisplatin's immunogenic properties [51].

Cisplatin-Induced Immunogenic Cell Death in HNSCC

Cisplatin, a platinum-based chemotherapeutic agent, is widely utilized in the treatment of head and neck squamous cell carcinoma due to its potent cytotoxic effects, primarily mediated through DNA crosslinking and apoptosis induction. By forming intra- and interstrand crosslinks within the genomic DNA of tumor cells, cisplatin disrupts essential replication and transcription processes, ultimately leading to cell cycle arrest and programmed cell death [4]. While its efficacy as a cytotoxic agent is

well-established, emerging evidence suggests that cisplatin possesses additional immunomodulatory properties, contributing to its therapeutic potential beyond direct tumor cell eradication [52]. A key immunogenic mechanism associated with cisplatin treatment is the induction of immunogenic cell death, a specialized form of apoptosis that elicits an adaptive immune response through the release of damage-associated molecular patterns [53]. These molecular signals, including extracellular ATP, high-mobility group box 1, and surface-exposed calreticulin, act as potent immunostimulatory agents, facilitating dendritic cell activation and subsequent tumor antigen presentation [54]. The activation of dendritic cells in response to these damage-associated molecular patterns enhances $CD8^+$ T-cell priming, thereby promoting robust antitumor immunity [55]. This immunogenic facet of cisplatin-mediated cell death distinguishes it from conventional apoptosis and underscores its role as a potential enhancer of immune checkpoint inhibition strategies [56].

Despite the promising immunogenic properties of cisplatin, its efficacy in head and neck squamous cell carcinoma is often compromised by the presence of an immunosuppressive tumor microenvironment [57]. Tumor-associated regulatory T cells and myeloid-derived suppressor cells exert immunosuppressive effects that impede effective antitumor immunity, diminishing the ability of $CD8^+$ T cells to mount sustained cytotoxic responses [58]. Additionally, the upregulation of immune checkpoint molecules such as programmed death-ligand within the tumor microenvironment facilitates immune evasion, reducing the effectiveness of cisplatin-induced immunogenic signalling [59]. Consequently, therapeutic interventions aimed at counteracting immune suppression within the tumor microenvironment, including immune checkpoint inhibitors and selective depletion of immunosuppressive cell populations, may synergize with cisplatin treatment to improve patient outcomes [60].

Another clinical challenge associated with cisplatin therapy is the emergence of resistance mechanisms, which limit its long-term efficacy [44]. Cisplatin-resistant tumor cells often exhibit enhanced DNA repair capabilities, effectively reversing cisplatin-induced DNA damage and restoring proliferative potential [61]. Additionally, increased expression of drug efflux transporters facilitates cisplatin extrusion from tumor cells, further contributing to therapeutic resistance. These resistance mechanisms underscore the need for combination strategies that integrate cisplatin with adjunctive therapies targeting DNA repair pathways or efflux-mediated drug resistance [59].

Anti-PD-L1 siRNA-Mediated Immune Checkpoint Blockade

The PD-1/PD-L1 signaling axis represents a fundamental immune checkpoint mechanism that contributes to immune evasion in head and neck squamous cell carcinoma [57]. Tumor cells frequently overexpress PD-L1, which interacts with PD-1 receptors on T cells, leading to the inhibition of T-cell activation and the induction of exhaustion [62]. This interaction suppresses antitumor immune responses, facilitating tumor progression and reducing the efficacy of immunosurveillance mechanisms [63]. Therapeutic strategies aimed at disrupting this pathway have demonstrated significant potential in restoring T-cell function and enhancing antitumor immunity [60]. Anti-PD-L1 small interfering RNA has emerged as a promising molecular tool for modulating immune checkpoint inhibition [64]. By selectively targeting PD-L1 mRNA, siRNA-mediated gene silencing reduces PD-L1 protein expression, thereby preventing tumor-mediated suppression of cytotoxic T cells [31, 65]. The resulting restoration of T-cell activity enhances immune-mediated tumor clearance and contributes to improved therapeutic outcomes in head and neck squamous cell carcinoma [66]. However, several barriers impede the effective delivery of siRNA-based therapeutics, including enzymatic degradation in circulation and suboptimal cellular uptake [23, 67]. The inherent instability of free siRNA molecules necessitates specialized delivery systems capable of providing protection against nucleases while ensuring efficient intracellular transport [68].

Liposomal encapsulation offers a viable solution to the challenges associated with siRNA delivery by providing a biocompatible and protective environment that shields siRNA from enzymatic degradation [69]. Liposome-mediated delivery can be facilitated through passive targeting mechanisms, leveraging the enhanced permeability and retention effect for tumor-specific accumulation [70]. Alternatively, active targeting strategies incorporate ligand-mediated uptake to improve siRNA internalization and enhance

therapeutic precision [71]. Surface modifications, including polyethylene glycol functionalization, further contribute to prolonged circulation times and reduced immune clearance, optimizing liposomal delivery of siRNA therapeutics [26].

Synergistic Effects of Cisplatin and siRNA Co-Delivery

The concurrent delivery of cisplatin and anti-PD-L1 siRNA represents a multifaceted approach that integrates both cytotoxic and immunomodulatory mechanisms to enhance tumor clearance in head and neck squamous cell carcinoma. Cisplatin, a platinum-based chemotherapeutic agent, exerts its antitumor activity primarily through the induction of DNA crosslinking, leading to apoptosis and immunogenic cell death [72]. This process is characterized by the release of damage-associated molecular patterns, including extracellular ATP, high-mobility group box 1, and surface-exposed calreticulin, which facilitate dendritic cell activation and antigen presentation. As a result, cisplatin treatment initiates a cascade of immune responses that culminate in $CD8^+$ T-cell priming and enhanced tumor infiltration [73]. Despite the immunogenic properties of cisplatin, the immunosuppressive tumor microenvironment often limits its efficacy by promoting T-cell exhaustion and suppressing cytotoxic activity [74]. Regulatory T cells and myeloid-derived suppressor cells, commonly found in head and neck squamous cell carcinoma, actively inhibit antitumor immunity, thereby reducing the therapeutic potential of cisplatin-induced immunogenic signalling [58]. The incorporation of anti-PD-L1 siRNA within the treatment paradigm addresses this limitation by silencing PD-L1 expression in tumor cells and immune compartments, thereby restoring T-cell functionality and preventing immune suppression. PD-L1, a key immune checkpoint molecule, interacts with PD-1 on T cells to inhibit their activation and promote functional exhaustion [75]. The downregulation of PD-L1 through siRNA-mediated mRNA degradation disrupts this immune checkpoint pathway, reinvigorating cytotoxic T-cell responses and augmenting the immunogenic effects of cisplatin therapy [76].

Chenyu Li et al [77], checked and concluded that nanomaterials are being prominently utilized in the realm of nanomedicine because of their extremely good properties, especially inside the context of cancer detection and remedy. within the context of HNC treatment, nanomaterials have demonstrated the capacity to reinforce the effectiveness of chemotherapy whilst minimizing associated toxicities. The usage of nanoparticles as carriers for drug delivery in HNC has opened up avenues to alleviate affected person suffering and extend the lives of these with superior-stage disease.

CONCLUSION AND FUTURE PERSPECTIVES

The emergence of dual-ligand liposomal formulations incorporating cisplatin and anti-PD-L1 siRNA represents a promising strategy for enhancing immune checkpoint modulation and chemotherapy efficacy in head and neck squamous cell carcinoma. This approach leverages cisplatin-induced immunogenic cell death to stimulate immune responses while simultaneously silencing PD-L1 expression to counteract tumor-associated immunosuppressive mechanisms. By employing ligand-mediated tumor-specific targeting, these nanoscale delivery systems improve drug accumulation, minimize systemic toxicity, and optimize intracellular therapeutic retention. Preclinical studies have demonstrated enhanced $CD8^+$ T-cell infiltration, reduced regulatory T-cell populations, and improved tumor regression with dual-ligand liposome co-delivery compared to monotherapy approaches, reinforcing the synergistic effects of integrating chemotherapy and immune checkpoint inhibition.

The introduction of dual-ligand nanocarrier systems addresses key limitations associated with conventional immune checkpoint inhibitors and platinum-based chemotherapy. The immunosuppressive tumor microenvironment, a major barrier to therapeutic efficacy in head and neck squamous cell carcinoma, can be reprogrammed through immune modulatory interventions incorporated into liposomal formulations. By selectively depleting myeloid-derived suppressor cells and repolarizing tumor-associated macrophages toward a pro-inflammatory phenotype, these systems enhance immune-mediated tumor clearance while mitigating the emergence of drug resistance. The ability of these liposomes to improve drug bioavailability and tumor-specific accumulation presents a viable strategy for reducing systemic toxicity, ensuring prolonged therapeutic exposure, and enhancing patient outcomes in clinical

settings.

To facilitate clinical translation, future investigations must focus on optimizing liposomal physicochemical properties, refining ligand selection, and evaluating therapeutic efficacy in relevant patient-derived tumor models. Further studies on formulation stability, controlled drug release kinetics, and biodistribution profiling are necessary to ensure reproducibility and scalability for clinical applications. Additionally, comparative analyses between dual-ligand liposomes and existing checkpoint blockade therapies will be instrumental in determining the advantages of this nanocarrier approach. Regulatory considerations for safety, biocompatibility, and immunogenic potential must also be addressed to enable progression into early-phase clinical trials. Ultimately, the integration of dual-ligand liposomes into personalized oncologic treatment strategies offers a novel paradigm for combinatorial precision medicine, bridging the gap between chemotherapy and immunotherapy to improve therapeutic outcomes for patients with head and neck squamous cell carcinoma.

CONFLICT OF INTEREST

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

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