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Nanoparticle-based drug delivery systems: opportunities and challenges in the treatment of esophageal squamous cell carcinoma (ESCC)

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Esophageal squamous cell carcinoma (ESCC) is an aggressive malignancy characterized by limited treatment options and poor prognosis. Nanoparticle-based drug delivery systems have emerged as a promising strategy to enhance cancer therapy efficacy by improving drug targeting, reducing toxicity, and enabling multifunctional applications. This review highlights some key types of nanoparticles, including liposomes, polymeric nanoparticles, metallic nanoparticles, dendrimers, and quantum dots, which could effectively improve the delivery of various drugs used in chemotherapy, radiotherapy, and immunotherapy, offering more precise and effective treatment options. With the ability to improve drug stability and overcome biological barriers, nanoparticle-based systems represent a transformative strategy for ESCC treatment. Despite some challenges, such as biocompatibility and scalability, the future of nanoparticle-based drug delivery holds great promise, particularly in the development of personalized nanomedicine and novel therapeutic approaches targeting the tumor microenvironment. With ongoing advancements, nanoparticle-based drug delivery systems hold immense potential to revolutionize ESCC treatment and improve patient outcomes.

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1. Introduction

Esophageal squamous cell carcinoma (ESCC) is an aggressive malignancy, which is often diagnosed at advanced stages due to the absence of early symptoms, resulting in a poor prognosis and high mortality rates, particularly in Asia and Africa.^{1,2} Characterized by unique pathological features, ESCC progresses through a multistep process driven by genetic and epigenetic alterations.³ Environmental factors such as tobacco use,⁴ heavy alcohol consumption,^{5,6} consumption of hot beverages,⁷ and dietary deficiencies⁸ are some major triggers. Chronic inflammation, such as esophagitis, further predisposes the esophageal lining to malignant transformation.⁹ Key mutations in tumor suppressor genes like TP53 and oncogenes such as PIK3CA promote uncontrolled cell proliferation and inhibit apoptosis.^{10–13} The tumor microenvironment, comprising cancer-associated fibroblasts and immune cells, creates barriers to drug penetration and foster tumor progression through various mechanisms.^{14–17} Additionally, hypoxic conditions within the tumor core reduce sensitivity to radiation and chemotherapy while driving angiogenesis and meta-

stasis.¹⁸ The limitations of current treatments, including surgery, chemotherapy, radiotherapy, and immunotherapy still exist, highlighting the urgent need for more precise and less toxic approaches^{19–22} (Fig. 1).^{6,23,24}

Nanoparticle-based drug delivery systems provide an innovative solution to overcome the limitations of conventional cancer therapies. These systems enhance drug delivery by improving the precision, efficiency, and safety of treatment. Engineered nanoparticles specifically target tumor cells, reducing off-target effects and enhancing therapeutic outcomes.²⁵ Their small size and modifiable surface properties allow enhanced permeability and retention (EPR) within tumors, enabling superior accumulation in tumor tissues compared to normal tissues.^{23,26,27} This property is particularly beneficial for treating difficult-to-reach cancers like ESCC. In ESCC, the challenges of treatment failure are multifactorial, involving factors such as treatment resistance, tumor heterogeneity, recurrence, and inadequate drug penetration. Nanoparticles can address some of these challenges by improving drug delivery and targeting. Moreover, nanoparticles offer multifunctional applications, such as theranostics, which integrates therapy and diagnostics in a single platform. These advanced systems allow for simultaneous drug delivery, imaging, and real-time monitoring of treatment responses, providing a more integrated approach to cancer therapy.^{28,29} For example, nano-

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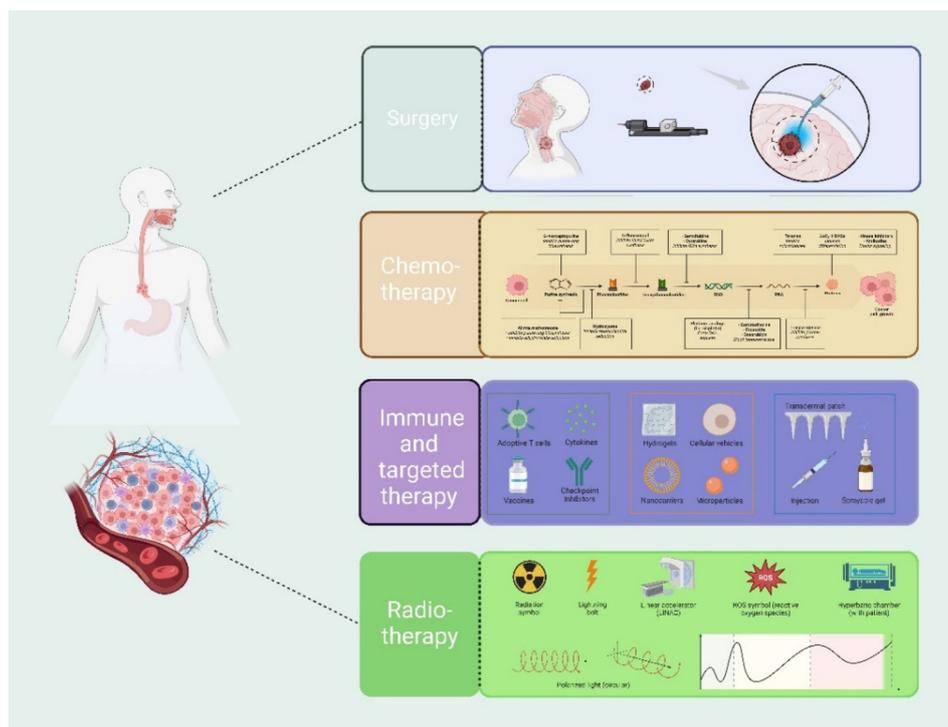


Fig. 1 Overview of current treatment approaches for esophageal squamous cell carcinoma. Created with biorender.com. Reprinted with permission from ref. 6, 23 and 24, Copyright © 2023, 2022 and 2021, Frontiers In Immunology, Signal Transduct Target Ther and Elsevier.

particles can be loaded with chemotherapeutic agents while being functionalized with contrast agents for imaging,^{30–32} enabling clinicians to track the drug distribution and efficacy in real-time.

Despite these promising benefits, nanoparticle-based drug delivery systems face challenges, including biocompatibility, potential toxicity, and difficulties in large-scale manufacturing and quality control. This review explores various types of nanoparticles employed in drug delivery, their applications in ESCC treatment, and the steps needed for successful clinical implementation.

2. Types of nanoparticle-based drug delivery systems

Nanoparticle-based drug delivery systems offer diverse structures and functionalities that enhance the therapeutic potential of anticancer agents. These nanoparticles can be customized in terms of size, shape, surface properties, and composition to suit specific therapeutic needs. The following are some of the most commonly applied types of nanoparticles in drug delivery systems, and Fig. 2 provides an overview of the various types and classifications of nanoparticles.³³

2.1 Liposomes

Liposomes are composed of phospholipids, such as phosphatidylcholine and cholesterol, forming spherical vesicles with

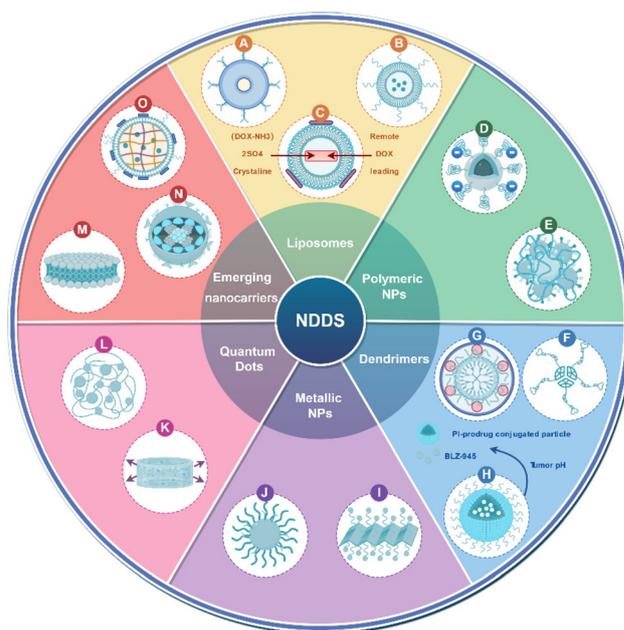


Fig. 2 Types of nanoparticles in drug delivery. Created by Figdraw. License ID: AerS=e8d2c. Reprinted with permission from ref. 32. Copyright © 2024, ACS Omega.

lipid bilayers that can encapsulate hydrophilic drugs in their aqueous core and hydrophobic drugs within the bilayer.^{34–37} Their mechanism of action involves several key processes:



encapsulating drugs to protect them from degradation,³⁸ prolonging circulation time through PEGylation to evade immune clearance,³⁹ and exploiting the Enhanced Permeability and Retention (EPR) effect to passively target tumor tissues by accumulating in their leaky vasculature.^{40–42}

Liposomes can also be engineered for active targeting by attaching ligands or antibodies that bind to cancer-specific receptors, facilitating precise drug delivery to tumors. Liu *et al.* developed a biomimetic liposome nano-platinum system (nano-Pt/VP@MLipo) that combines the peroxidase-like activity of platinum nanoparticles (nano-Pt), which are encapsulated in the aqueous core of the liposomes, while the photosensitizer verteporfin (VP) is loaded into the lipid bilayer. The liposomes are further hybridized with macrophage cell membranes, imparting biomimetic and targeting properties, which enhance tumor penetration and chemotherapy efficacy.⁴³ Additionally, stimuli-responsive liposomes release their drug payload in response to the acidic tumor microenvironment, ensuring minimal release in healthy tissues. The composition of liposomes can be adjusted to control drug release, enabling sustained delivery over time. This combination of protective encapsulation, targeted delivery, and controlled release makes liposomes highly effective in cancer therapy, improving drug bioavailability while minimizing systemic toxicity. Research has developed pH-sensitive liposomes (IRI&398-s-LPs) for the combined delivery of irinotecan (IRI) and NVP-BGJ398 (398). These liposomes are designed to release both drugs under the acidic conditions of the tumor microenvironment. The compound 398 targets FGFR on the surface of cancer-associated fibroblasts (CAFs) and inhibits their activity, while IRI induces apoptosis in tumor cells. This combination therapy aims to eliminate the “seeds” (tumor cells) and reshape the “soil” (CAFs) to enhance the treatment of colorectal cancer.⁴⁴

2.2 Polymeric nanoparticles

Polymeric nanoparticles, made from biocompatible and biodegradable polymers,^{45,46} such as poly(lactic-*co*-glycolic acid) (PLGA)^{47–49} or chitosan,^{50,51} provide a versatile platform for drug delivery due to their ability to encapsulate drugs and offer controlled, sustained release. These nanoparticles protect drugs from degradation and allow for precise release over time as the polymer matrix degrades.^{52–54} In cancer therapy, polymeric nanoparticles can be engineered to release drugs in response to the acidic tumor microenvironment, taking advantage of the lower pH to trigger targeted drug release.⁵⁵ This pH-sensitive design enhances drug accumulation at the tumor site while minimizing release in healthy tissues, reducing systemic toxicity.⁵⁶ A study has developed polymeric nanoparticles coated with hyaluronic acid (HA), utilizing a double polymer shell made of poly(lactic-*co*-glycolic acid) (PLGA) and poly(glycolic acid) (PSAR) to target CD44 receptors overexpressed in colorectal cancer cells. The optimized nanoparticles demonstrated enhanced controlled release of the drug, excellent cytotoxicity against the HCT116 cell line, improved pharmacokinetics *in vivo*, as well as effective targeting and biocompatibility.⁵⁷ Additionally, the nanoparticles can

passively target tumors *via* the Enhanced Permeability and Retention (EPR) effect and can be further functionalized with ligands or antibodies for active targeting of cancer cell receptors, ensuring higher specificity.⁵⁸ These combined properties make polymeric nanoparticles particularly effective for cancer treatment by improving drug bioavailability, targeting tumors precisely, and minimizing harmful side effects.

2.3 Metallic nanoparticles

Metallic nanoparticles, particularly gold and silver nanoparticles, are composed of metal cores that provide unique optical, electronic, and physical properties due to their high surface area and tunable plasmonic resonance.^{59–61} These properties enable them to absorb and convert light energy into heat, a key mechanism in photothermal therapy.^{62–64} In cancer treatment, gold nanoparticles can be engineered to target tumor cells through surface functionalization with ligands or antibodies that bind to specific cancer cell receptors.^{65,66} Once localized at the tumor site, these nanoparticles are irradiated with near-infrared light, which they absorb and convert into localized heat, leading to the destruction of cancer cells through hyperthermia.^{67–69} This process selectively kills tumor cells while sparing healthy tissue due to the precise targeting and localized heat generation. Additionally, metallic nanoparticles can be functionalized with chemotherapeutic drugs, allowing for a dual approach in which both chemotherapy and photothermal therapy are employed.^{70,71} The nanoparticles serve as drug carriers, releasing the chemotherapy agent at the tumor site while simultaneously enhancing the therapeutic effect through heat generation.^{72–74} This combination of targeted drug delivery and photothermal therapy maximizes tumor destruction and minimizes damage to surrounding healthy tissues, making metallic nanoparticles a powerful tool in cancer treatment.

2.4 Dendrimers

Dendrimers are nanoscale, highly branched, tree-like polymers composed of a central core, repeated branching units, and numerous terminal functional groups.⁷⁵ Their unique, well-defined structure provides a high degree of control over drug loading and release, as each branching point and surface functional group offers multiple attachment sites for therapeutic agents, imaging molecules, or targeting ligands.⁷⁶ In cancer treatment, dendrimers can be designed to simultaneously carry chemotherapeutic drugs, gene therapies, and even diagnostic agents within a single platform.^{77,78} Their precise structure allows for controlled and sustained release of these agents, improving drug stability and reducing off-target effects.⁷⁹ Additionally, the nanoscale size and high surface area-to-volume ratio of dendrimers enable them to penetrate biological barriers, such as the tumor microenvironment and cellular membranes, allowing for enhanced accumulation in tumor tissues.^{80–83} Functionalization with specific ligands or antibodies further enhances their ability to selectively target cancer cells, ensuring that therapeutic agents are delivered directly to the tumor. This combination of multi-functional



drug delivery, precise targeting, and effective penetration makes dendrimers a powerful and versatile tool for cancer treatment, capable of delivering complex, multi-agent therapies while minimizing systemic toxicity and side effects.

2.5 Quantum dots and emerging nanocarriers

Quantum dots are nanoscale semiconductor particles, typically composed of materials like cadmium selenide (CdSe) or indium phosphide (InP), that exhibit unique optical properties due to quantum confinement effects.⁸⁴ These properties allow quantum dots to emit bright, size-tunable fluorescence when excited by light, making them valuable for both imaging and drug delivery applications.^{85,86} In cancer therapy, quantum dots can be conjugated with therapeutic drugs or targeting ligands on their surface to selectively bind to tumor-specific receptors.^{87,88} This dual functionality enables real-time imaging of drug distribution while delivering the therapeutic payload to the tumor site.⁸⁹ Quantum dots can track the movement and accumulation of drugs in tumor tissues, offering precise monitoring of treatment efficacy.^{90,91} Additionally, their high surface-to-volume ratio allows for the attachment of multiple therapeutic agents, enhancing their versatility in multi-drug delivery systems. In cancer theranostics, quantum dots integrate diagnosis and therapy into a single platform, providing both imaging for diagnosis and targeted treatment.^{92,93} Alongside quantum dots, other nanocarriers like carbon nanotubes and nanogels are being investigated for their ability to deliver drugs with high precision and efficiency, exploiting their unique structures for enhanced drug loading, controlled release, and targeted delivery, further advancing cancer treatment strategies.^{94–98}

These various types of nanoparticles each offer distinct advantages in drug delivery. By carefully selecting the type of nanoparticle based on the desired therapeutic outcome, researchers can optimize drug delivery to improve the effectiveness of ESCC treatment while reducing side effects.

3. Applications of nanoparticle drug delivery systems in ESCC

Nanoparticle-based drug delivery systems significantly enhance the treatment of ESCC by improving drug targeting, therapeutic efficacy, and reducing systemic toxicity. Table 1 provides an overview of nanoparticle drug delivery systems currently utilized in chemotherapy and radiotherapy and Table 2 presents a comprehensive overview of the nanoparticle drug delivery systems that are currently employed in gene therapy and immunotherapy for ESCC.

3.1 Advancements in chemotherapy

Current chemotherapy regimens for ESCC typically involve combination therapies to enhance efficacy and minimize resistance. Cisplatin, often paired with fluorouracil (5-FU) or taxanes such as paclitaxel or docetaxel, remains a key component in the first-line treatment.⁹⁹ These combinations are

administered *via* intravenous infusion and are designed to target cancer cells through multiple mechanisms. Cisplatin exerts its anticancer effects by forming cross-links in DNA, which leads to mispairing of nucleotides and ultimately triggers apoptosis in cancer cells. Similarly, fluorouracil (5-FU) disrupts DNA synthesis by inhibiting thymidylate synthase, while taxanes stabilize microtubules to prevent cell division, contributing to apoptosis.¹⁰⁰ Despite the effectiveness of these chemotherapy regimens, resistance remains a significant barrier to successful treatment in ESCC. Despite its effectiveness, cisplatin monotherapy is often hindered by systemic toxicity and the development of drug resistance,^{101–103} drug resistance in ESCC can be attributed to several factors. One primary factor is the increased efflux of drugs from cancer cells, mediated by the upregulation of ATP-binding cassette (ABC) transporters, which limits the accumulation of therapeutic agents within the cells. Additionally, the overexpression of DNA repair proteins, such as excision repair cross-complementation group 1 (ERCC1), enables cancer cells to effectively repair DNA damage caused by these therapies, thereby preventing apoptosis. Impaired drug uptake is another critical factor contributing to resistance.¹⁰⁴ For instance, decreased expression of nucleoside transporters like hENT1 hampers the intracellular accumulation of drugs, while elevated levels of glutathione serve to detoxify and neutralize the therapeutic agents, further diminishing their effectiveness.^{105,106} Furthermore, alterations in apoptotic pathways and the activation of stress response mechanisms can also complicate treatment outcomes.^{107,108} Together, these resistance mechanisms present significant challenges to the efficacy of current ESCC chemotherapy regimens, necessitating the exploration of novel therapeutic strategies to overcome these barriers and improve patient outcomes.

To address these limitations, nanoparticle-based delivery systems have emerged as a promising solution. Nanomaterials can target resistance genes and enhance the delivery of chemotherapy drugs, acidic environment, thereby improving targeting and intracellular delivery.¹³⁴ In the context of first-line chemotherapy regimens, combinations such as the FOLFOX (oxaliplatin, 5-FU, leucovorin) and CROSS (carboplatin, paclitaxel) have also been investigated. The addition of nanoparticles to these regimens holds promise for further enhancing treatment outcomes.¹³¹ Researchers have also explored chemical modifications of chemotherapy drugs to improve their delivery, targeting functions, and reduce toxicity. A novel four-way junction RNA nanoparticle carrier-4WJ-EGFRapt-miR-375-PTX was developed to simultaneously deliver miR-375 and the chemotherapy drug paclitaxel (PTX), decorated with epidermal growth factor receptor (EGFR) specific aptamers (EGFRapt). This nanoparticle exhibited good thermal and pH stability, with EGFRapt modification enhancing tumor cell endocytosis and deep penetration into three-dimensional ESCC spheroids. In an ESCC xenograft mouse model, this nanoparticle selectively distributed to tumor sites through EGFRapt-mediated active targeting, showing more effective therapeutic efficacy with co-delivery of miR-375 and PTX while exhibiting lower systemic toxicity¹³⁰ (Fig. 3a).



Table 1 Overview of nanoparticle drug delivery systems currently applied in chemotherapy and radiotherapy for ESCC

Type	NP	Assessment	Mechanism	Limitations	Ref.
Chemotherapy	PEGylated nanoliposome	<i>In vitro</i> and <i>in vivo</i>	-Enhances drug concentration in tumor cells through receptor-mediated uptake, improving efficacy; rapid release of LY294002 inhibits autophagy in tumor cells, increasing their sensitivity to 5-FU	-Oversized particles may affect biodistribution and targeting; <i>in vivo</i> stability and drug release properties lack detailed explanation	109
	FA-M(PTX)	<i>In vitro</i> and <i>in vivo</i>	-The FA-M(PTX) effectively inhibit the growth of ESCC xenografts and extend the survival of tumor-bearing nude mice by inducing apoptosis through the regulation of Bax, Caspase 3, and Bcl2 expression	-The difference in antitumor activity between <i>in vitro</i> and <i>in vivo</i> studies may result from the rapid clearance of free paclitaxel and the "shielding" effect of the nanoparticles	110
	Hollow carbon spheres (HCSs)	<i>In vitro</i> and <i>in vivo</i>	-Efficiently delivers the chemotherapy drug doxorubicin to tumor sites; exhibits good biocompatibility, evading lysosomal degradation, and extends drug circulation time, altering biodistribution to increase tumor accumulation	-Potential biohazards and health or environmental impacts significantly limit its clinical use; the drug loading capacity needs further improvement	111
	DSPE-PEG2000 nanoliposomes	<i>In vitro</i> and <i>in vivo</i>	-DOX and ORD induce tumor cell apoptosis by inhibiting the PI3K/AKT/mTOR and Ras/Raf signaling pathways; nano-liposomal carriers enhance the targeting and permeability of the drugs in tumor tissues	The release profile under different pH conditions and the absorption and distribution characteristics <i>in vivo</i> need to be evaluated	112
	bMED NPs	<i>In vitro</i> and <i>in vivo</i>	-Efficiently co-delivers doxorubicin and β -elemene, releasing them in optimal ratios for enhanced combination therapy; targets tumors with prolonged circulation, increasing drug accumulation; induces apoptosis by upregulating Bax, downregulating Bcl-2, and raising apoptosis rates	-Some toxicity to normal organs remains; tumor accumulation still needs improvement	113
	TAB-CIS/5-FU LPHNs	<i>In vitro</i> and <i>in vivo</i>	-CIS and 5-FU exhibit synergy in lipid-polymer hybrid nanoparticles (LPHNs); TAB modification boosts nanoparticle uptake by tumor cells; LPHNs allow slow release of CIS and 5-FU, increasing tumor drug concentration	-Release behavior and kinetics need further optimization; optimal drug ratios for synergy require further exploration	114
	CM- β -CD-PEI-PEG-T7/DTX/CUR (T7-NP-DC)	<i>In vitro</i> and <i>in vivo</i>	-Chemotherapy drugs like gemcitabine, doxorubicin, and paclitaxel enhance immune effects by inducing immunogenic cell death and clearing myeloid-derived suppressor cells. Improve cellular uptake and tumor targeting, increasing therapeutic efficacy; these drugs prolong half-life and boost tumor accumulation with pH-responsive release	-Insufficient data on the impact of nanoparticles on the tumor immune microenvironment; only short-term biocompatibility studies were conducted	115
	RGD-f-PNP/EPI	<i>In vitro</i> and <i>in vivo</i>	-EPI-loaded RGD-f-PNPs enable monitoring of drug delivery and effects <i>via</i> near-infrared fluorescence	-Further studies are needed on biological performance, biodistribution, stability, and targeting <i>in vivo</i>	116
	PEG-TE 10 @PLGA@DOX-Cur NP (PMPN)	<i>In vitro</i> and <i>in vivo</i>	-Cancer cell membrane-coated PLGA nanoparticles with DOX and Cur target multidrug-resistant esophageal cancer, inhibiting tumor growth <i>in vitro</i> and <i>in vivo</i>	-The preparation is complex, and further animal and clinical trials are required to assess safety and efficacy	117



Table 1 (Contd.)

Type	NP	Assessment	Mechanism	Limitations	Ref.
Radiotherapy	PLGA (poly(lactic-co-glycolic acid)) nanoparticles	<i>In vitro</i> and <i>in vivo</i>	-Encapsulating ¹¹¹ In and Ru1 in PLGA nanoparticles enhances DNA damage and cytotoxicity, targeting EGFR-overexpressing tumor cells more effectively	-Toxicity, complex preparation, and <i>in vivo</i> stability, pharmacokinetics, and efficacy need further validation	118
	TADI-COF-Fc	<i>In vitro</i> and <i>in vivo</i>	-Contains iodine for X-ray absorption and a chromium-phenanthroline (Fc) group for disrupting redox balance and inducing ferroptosis; enhance lipid peroxidation and ferroptotic cell death, effective <i>in vitro</i> and <i>in vivo</i>	-The small size (about 110 nm) may impact biodistribution and tumor targeting, and there is inadequate data on <i>in vivo</i> metabolism and toxicity	119
	GDY-CeO ₂ nanocomposites	<i>In vitro</i> and <i>in vivo</i>	-miR181a enhances the sensitivity of the ESCC cell line KYSE30 to radiotherapy; induces DNA damage and apoptosis to overcome radioresistance	-CeO ₂ nanoparticles tend to aggregate, reducing activity; bioavailability and biocompatibility need improvement	120
	iE-PRNPs	<i>In vitro</i>	-Significant effects in esophageal cancer cells with high and low EGFR through G2/M phase arrest, increased reactive oxygen species, and enhanced DNA double-strand breaks	-The low G2/M phase arrest may relate to slow drug release and IC15 concentration; further research is needed for clinical translation	121
	MnSe ₂ -lipid	<i>In vitro</i> and <i>in vivo</i>	-Activates the cGAS-STING pathway, promoting the upregulation of p-IRF3, IFN-β, and CXCL10; enhances antitumor immune responses, reduces radiotherapy side effects, and improves treatment efficacy	-The primary mechanism is limited to the tumor environment; biocompatibility and metabolism in normal tissues are needed	122
	FA-BSA-Au@PTX/CUR	<i>In vitro</i>	-Concentrating ionizing radiation produces more cytotoxic secondary charged particles, maximizing X-ray damage to tumors. The G2/M phase is most sensitive to ionizing radiation; paclitaxel (PTX) induces G2/M arrest and acts as a radiosensitizer	-Further investigation of radiosensitization is needed, along with optimization of complex preparation, large-scale production, and long-term safety	123
	AuNPs-D-P-DA	<i>In vitro</i> and <i>in vivo</i>	-AuNPs aggregate, enhancing accumulation and improving radiosensitization, DNA damage, apoptosis, and antitumor effects through fatty acid oxidation (FAO) in the acidic tumor microenvironment	-Excessive aggregation may reduce permeability and radiosensitization. Further studies are needed to optimize administration routes, doses, and toxicity	73
	EBRT and Rhenium-188 (¹⁸⁸ Re)-liposome	<i>In vitro</i> and <i>in vivo</i>	-EBRT enhances the accumulation of ¹⁸⁸ Re-liposomes in tumors, liver, and feces, possibly increasing tumor sensitivity to radioactive isotopes	-May harm the lower urinary tract and gastrointestinal system	124
	Au ₈ (C ₂₁ H ₂₇ O ₂) ₈ (Au ₈ NC)	<i>In vitro</i> and <i>in vivo</i>	-Generate reactive oxygen species (ROS) under X-ray exposure leads to irreversible apoptosis in cancer cells	-Long-term biosafety needs evaluation; preparation should be optimized for cost, reproducibility, and scalability	125

Overall, the integration of nanoparticles into chemotherapy for ESCC represents a significant advancement. These systems not only enhance drug delivery and efficacy but also mitigate the adverse effects commonly associated with traditional therapies. The successful clinical application of nanoparticle formulations, such as nab-paclitaxel, underscores the potential of this innovative approach in transforming the treatment landscape for ESCC, particularly within first-line chemotherapy regimens, ultimately improving patient outcomes.

3.2 Synergistic approaches with radiotherapy

Currently, radiotherapy (RT) plays a crucial role in the treatment of ESCC, often used in conjunction with chemotherapy

to enhance efficacy. These treatment strategies aim to enhance antitumor effects through synergistic actions. The mechanisms of radiotherapy ineffectiveness include the enhanced DNA repair capacity of tumor cells, hypoxic microenvironments that reduce radiation sensitivity, and cell cycle regulation allowing evasion of damage. Tumor cells may neutralize reactive oxygen species (ROS) from radiotherapy by increasing antioxidant enzymes,¹³⁵ while fibroblasts and immune cells in the tumor microenvironment also impact effectiveness.^{136,137} Tumor cells can escape immune surveillance by downregulating antigen expression or secreting immunosuppressive factors.¹³⁸ Cellular heterogeneity results in inconsistent responses to radiotherapy, with some resistant cells surviving treatment and prolifer-



Table 2 Overview of nanoparticle drug delivery systems currently applied in gene therapy and immunotherapy for ESCC

Type	NP	Assessment	Mechanism	Limitations	Ref.
Gene therapy	Thermosensitive gel-nano	<i>In vitro</i> and <i>in vivo</i>	-Use siRNA to inhibit BACH1 and restore T-cell antitumor immunity; REACTIVATE mutant p53 with PRIMA-1 to inhibit tumor growth	-Long-term stability, degradation <i>in vivo</i> , and targeting and efficacy require further study	126
	Lipid nanovector (EYLN)	<i>In vitro</i> and <i>in vivo</i>	-siRNA targeting LPCAT1 (siLPCAT1) is combined with EYLN coated in leukocyte membranes to form mEYLNs-Dox/siLPCAT1, enhancing cell uptake, tumor targeting, and circulation time	-May trigger immune rejection and faces challenges in preparation and large-scale production	127
	GDY-CeO ₂ nanocomposites	<i>In vitro</i> and <i>in vivo</i>	-Loading miR181a onto GDY-CeO ₂ nanozymes enhances radiotherapy by targeting RAD17; PEG-iRGD improves tumor targeting and penetration	-Tend to aggregate, reducing activity; improvements in bioavailability and biocompatibility are needed	120
	Photoactivated DNA nanodrug (MCD@TMPyP4@DOX)	<i>In vitro</i> and <i>in vivo</i>	-Target tumor mitochondria using MUC1 and CytC affinity; under near-infrared light, the nanodrug generates ROS, damaging mitochondria, reducing ATP levels, inhibiting P-gp activity, and releasing P-gp DNzyme to cleave MDR1 mRNA and suppress P-gp expression	-May affect blood cell counts; preparation and administration need optimization for better stability and therapeutic outcomes	128
	Protamine sulfate-nanodiamond hybrid nanoparticles	<i>In vitro</i>	-PS@ND nanoparticles delivering miR-203 suppressed Ran and DNP63 expression, inhibiting esophageal cancer cell proliferation and migration	- <i>In vivo</i> efficacy and safety are untested, and large-scale production feasibility remains unclear, potentially limiting clinical application	129
Immunotherapy	Four-way junction RNA nanocarrier, 4WJ-EGFRapt-miR-375-PTX	<i>In vitro</i> and <i>in vivo</i>	-Decorated with an EGFR-specific aptamer (EGFRapt), enhances tumor targeting and penetrates 3D ESCC spheroids by promoting endocytosis	-Uniform tumor penetration leads to uneven drug distribution and reduced efficacy	130
	Lipid Nanoparticles (LNPs)	<i>In vitro</i> and <i>in vivo</i>	-Inhibit PD-L1 expression to boost antitumor immunity <i>via</i> gene silencing; stimulate the immune system and enhance chemotherapy for tumor treatment	-Long-term stability and biocompatibility need evaluation, and drug loading and encapsulation efficiency need improvement	131
	ITFn-Pt(IV)	<i>In vitro</i> and <i>in vivo</i>	-Integrate PD-L1 blockade, chemotherapy, and T-cell activation; enhance T-cell response and tumor infiltration	-Long-term efficacy and safety are needed to evaluate	132
	OTS964/Ce6@NP	<i>In vitro</i> and <i>in vivo</i>	-Induce significant infiltration of natural killer (NK) cells into the tumor microenvironment, triggering a robust antitumor immune response	-Further studies on other immune cells are needed, and preparation processes and drug loading efficiency require optimization for better <i>in vivo</i> stability and drug release	133

ating again.^{139,140} These mechanisms collectively diminish the efficacy of radiotherapy, highlighting the need for new therapeutic strategies to overcome resistance.

To overcome these resistance mechanisms in ESCC, the integration of nanoparticles shows significant potential. Nanoparticles can increase tumor cell sensitivity to radiation, thereby improving therapeutic outcomes. For example, gold nanoparticles can enhance radiation sensitivity through localized thermal effects.¹²⁵ Additionally, nanoparticles can precisely deliver radioactive isotopes or radiosensitizers, minimizing damage to surrounding healthy tissues. Dai *et al.* developed a stable and enzyme-like GDY-CeO₂ nanocomposite by anchoring and dispersing cerium oxide (CeO₂) nanoparticles on graphdiyne (GDY). The GDY-CeO₂ nanozymes exhibit excellent catalase-like activity, effectively decomposing hydrogen peroxide into oxygen, thereby alleviating tumor hypoxia and enhancing the sensitivity of radiotherapy. Additionally, the nanocomposite is loaded with the miRNA miR181a, which

targets the DNA repair protein RAD17 to increase cellular sensitivity to radiation. To further enhance delivery to tumor sites, the nanocomposite is modified with the tumor-targeting peptide iRGD. This multipronged strategy utilizing GDY-CeO₂ nanozymes and miR181a demonstrates improved therapeutic efficacy both *in vitro* and *in vivo*¹⁴¹ (Fig. 3b). Moreover, multifunctional nanoparticles with imaging capabilities can enable real-time monitoring of tumor responses to radiotherapy, providing important support for personalized treatment.¹⁴² These studies indicate that the strategy of combining nanoparticles with radiotherapy offers new solutions to overcome resistance and enhances overall treatment effectiveness.

3.3 Innovations in gene therapy

Gene therapy represents a promising approach for treating ESCC by targeting genetic mutations or modulating gene expression. However, the effective delivery of nucleic acids, such as siRNA, miRNA, and CRISPR/Cas9 components, poses



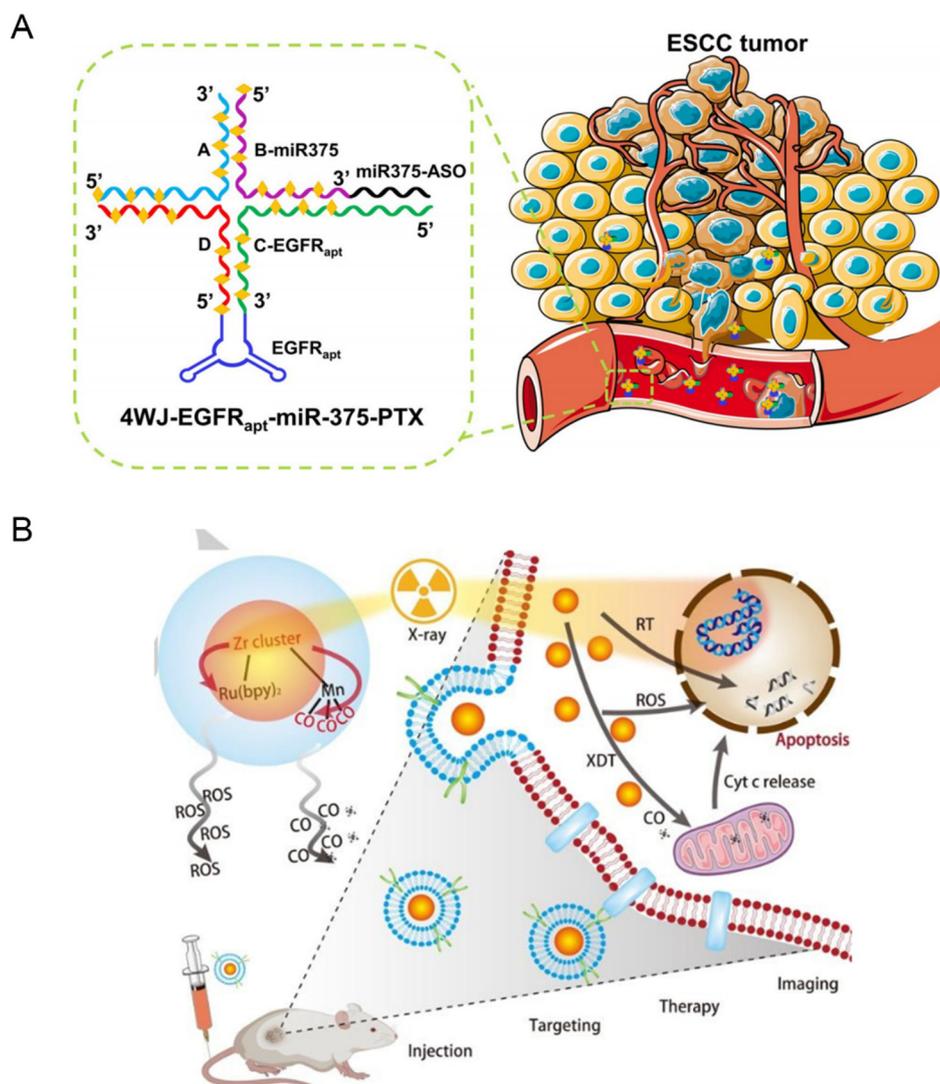


Fig. 3 (A) Schematic of the 4WJ-EGFRapt-miR-375-PTX nanoparticle, enhancing tumor targeting and co-delivering miR-375 and paclitaxel (PTX) for improved therapy and reduced toxicity in ESCC. (B) Schematic of ZrRuMn MONs@mem mechanisms *in vitro* and *in vivo*. Upon targeting, the nanoparticles demonstrate strong XDT and CO therapy, with enhanced MRI under X-ray irradiation. Reprinted with permission from ref. 126 and 137, Copyright © 2021 and 2022, JNAN and Angew. Chem. Int. Ed.

significant challenges due to their instability in the bloodstream and difficulty penetrating cell membranes.^{143–145} Nanoparticle-based delivery systems offer a potential solution, protecting nucleic acids from enzymatic degradation and enhancing their cellular uptake. These systems function through various mechanisms, protecting them from enzymatic degradation while improving bioavailability.

A key mechanism involves targeted gene delivery *via* receptor-mediated endocytosis, where nanoparticles are functionalized with ligands or aptamers that bind to overexpressed receptors on ESCC cells, such as EGFR. This enables selective entry into cancer cells, ensuring that gene therapy materials are delivered precisely to the tumor. For instance, the 4WJ-EGFRapt-miR-375-PTX system leverages EGFR-mediated targeting to co-deliver miR-375 and paclitaxel (PTX), effectively

inhibiting tumor proliferation, migration, and invasion.¹³⁰ Another critical mechanism is gene silencing *via* RNA interference. Nanoparticles are used to deliver small interfering RNA (siRNA) or microRNA (miRNA), which bind to specific mRNA molecules, preventing their translation and leading to gene silencing. In one example, GDY-CeO₂ nanoparticles loaded with miR181a target the RAD17 gene, reducing RAD17 protein expression. This impairs the DNA repair capacity of cancer cells, making them more vulnerable to treatments like radiotherapy.¹²⁰ Nanoparticle systems are also designed for stimuli-responsive gene release, triggered by the tumor micro-environment. These systems respond to specific stimuli, such as the acidic pH of tumors or the presence of overexpressed enzymes like matrix metalloproteinases (MMPs). This targeted release ensures that genetic materials are deployed only where



needed. For example, a photo-activated DNA nanomedicine (MCD@TMPyP4@DOX) uses photodynamic therapy (PDT) to generate reactive oxygen species (ROS), which trigger the nanomedicine to self-disassemble, releasing P-gp DNzyme to silence MDR1 mRNA. This process also inhibits P-glycoprotein (P-gp), which is involved in multidrug resistance (MDR), allowing chemotherapy drugs like doxorubicin (DOX) to accumulate in tumor cells more effectively.¹²⁸ In addition to gene delivery, nanoparticle systems help overcome drug resistance through combination therapy. For example, lipid nanocarriers such as mEYLN-Dox/siLPCAT1 co-deliver doxorubicin (DOX) and siRNA targeting the lipid metabolism gene LPCAT1, which is overexpressed in ESCC. This combined approach enhances the suppression of cancer cell proliferation, migration, and metastasis compared to single therapies, showing that combining gene therapy with chemotherapy can significantly improve therapeutic outcomes.¹²⁷

These mechanisms illustrate how nanoparticle-mediated gene therapy improves treatment efficacy in ESCC by enabling precise targeting, efficient delivery, and controlled release of genetic materials. By integrating these strategies, nanoparticle systems offer a promising future for gene therapy in cancer treatment.

3.4 Enhancements in immunotherapy and immune modulation

ESCC has seen advancements in immunotherapy, with key strategies including immune checkpoint inhibitors, such as pembrolizumab and nivolumab, targeting PD-1/PD-L1 pathways.^{21,146} These agents have shown promise, especially in patients with advanced ESCC, leading to improved survival rates in some clinical trials.¹⁴⁷ Combination therapies, incorporating chemotherapy or radiotherapy with immunotherapy, are also being explored to enhance therapeutic efficacy.^{148,149} However, immune therapy often encounters challenges leading to treatment failure. One major mechanism of resistance is the upregulation of immune checkpoint proteins, which inhibit T-cell activation and function.¹⁵⁰ Additionally, the tumor microenvironment in ESCC can be immunosuppressive, characterized by high levels of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) that impede anti-tumor immunity.¹⁵¹ Moreover, tumor heterogeneity and mutations in antigen presentation machinery can prevent effective recognition and targeting by immune cells.¹⁵² These factors contribute to the variable responses seen in patients and highlight the need for novel strategies to enhance immunotherapeutic effectiveness in ESCC.

Nanoparticles are emerging as a promising tool in enhancing immunotherapy for ESCC by improving the delivery of immunomodulatory agents and overcoming resistance mechanisms. The combination of the immune checkpoint inhibitor sintilimab with Nab-PTX and platinum-based drugs has shown considerable success as a first-line therapy for metastatic ESCC, achieving an objective response rate of 72.7% and a disease control rate of 90.9%.¹⁵³ Studies have shown that nanoparticle-based delivery systems can enhance immune

responses through various mechanisms. One key mechanism involves the induction of immunogenic cell death (ICD), where nanoparticles are engineered to improve immune cell activation. For example, research has developed a novel nanocomposite material called PBP@CpG, composed of black phosphorus functionalized with dopamine and loaded with the immune adjuvant CpG. This nanocomposite has been shown to trigger tumor cell death *via* a photoacoustic effect, leading to the release of tumor-associated antigens. These antigens promote dendritic cell maturation, boosting antigen presentation and eliciting a strong adaptive immune response. Additionally, PBP@CpG increases CD8+ T-cell infiltration into tumors and enhances the expression of IFN- γ and Granzyme B, improving the cytotoxic activity of both T-cells and natural killer cells. Furthermore, systemic immune responses are stimulated by this nanocomposite, which increases levels of TNF- α , IL-2, and IL-12 in the bloodstream, further strengthening the antitumor effect¹⁵⁴ (Fig. 4). Other studies have highlighted the potential of a thermosensitive gel nanoparticle system, which has been shown to increase T-cell infiltration and enhance immune response within the tumor microenvironment. This system boosts the ratio of CD4+ and CD8+ T-cells within tumor-infiltrating lymphocytes (TILs), while simultaneously reducing the number of T-regulatory cells (Tregs), which are known to suppress immune responses. After treatment with this gel nanoparticle system, IFN- γ levels increase significantly, indicating a potent antitumor immune response. Additionally, the gel system remains in the tumor for extended periods, leading to a prolonged and more effective immune response compared to conventional nanoparticles.¹²⁶ In terms of fusion immunotherapy systems, studies have introduced the ITFn-Pt(IV) system to enhance the immune response in ESCC by combining PD-L1 blockade, chemotherapy, and T-cell activation. This system uses temperature-regulated drug loading technology to create a smart delivery platform that releases T-cell activating peptides in response to the tumor microenvironment. It also incorporates PD-L1 nanobodies, which target and deliver platinum-based chemotherapy drugs directly to tumor cells, inducing immunogenic cell death and promoting dendritic cell maturation. Preclinical models of ESCC have demonstrated that this system significantly improves T-cell infiltration and antitumor efficacy without causing systemic side effects.¹³² Finally, lipid-core-shell nanoparticle platforms have been shown to co-deliver the FOLFOX chemotherapy regimen (miriplatin, 5-fluoro-2'-deoxyuridine-5'-monophosphate, and calcium leucovorin) along with siRNA targeting PD-L1. This approach enhances the efficacy of PD-1/PD-L1 immune checkpoint inhibition by blocking PD-L1 expression in tumor cells, overcoming chemoresistance, and boosting the infiltration of CD8+ T-cells and mature dendritic cells into the tumor microenvironment. These mechanisms work synergistically to promote a stronger immune response, significantly improving antitumor outcomes.¹³¹

In summary, immunotherapy for ESCC has advanced beyond traditional approaches by incorporating nanoparticle systems that utilize multiple mechanisms to enhance immune



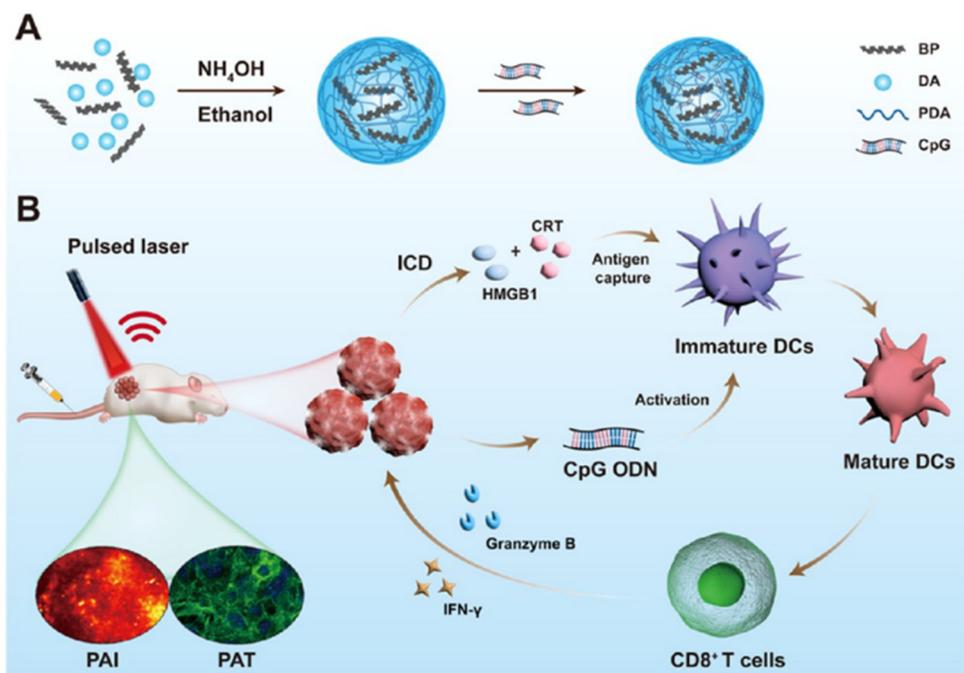


Fig. 4 (A) Schematic illustration of the synthesis of PBP@CpG, a multifunctional nanocomposite combining PBP and CpG for enhanced therapeutic effects. (B) PBP@CpG nanoparticles administered intravenously in mice, followed by tumor photoacoustic imaging and immunotherapy, demonstrating their potential for targeted cancer treatment. Reprinted with permission from ref. 150, Copyright © 2023, ACS.

responses. These mechanisms include inducing immunogenic cell death, promoting dendritic cell maturation, increasing T-cell infiltration, and targeting immune checkpoints such as PD-L1. Fig. 5 illustrates the immune microenvironment of esophageal squamous cell carcinoma (ESCC) and the role of nanoparticles in enhancing immunotherapy. By integrating these innovative strategies into clinical practice, nanoparticle-based immunotherapy has the potential to significantly improve treatment outcomes for patients with ESCC.

4. Challenges of nanoparticle-based drug delivery systems

While nanoparticle-based drug delivery systems offer promising advantages for treating ESCC, their clinical translation faces several significant challenges. These challenges include biocompatibility, targeting efficiency, manufacturing scalability, and potential toxicity. Addressing these challenges is crucial to fully realizing the therapeutic potential of nanoparticle systems.

4.1 Biocompatibility, metabolism, toxicity, and immune response

Ensuring the biocompatibility and safety of nanoparticles is essential for their clinical use. Nanoparticles should ideally be non-toxic, non-immunogenic, and biodegradable to minimize patient harm. Materials such as polymers, lipids, and metals should degrade without generating harmful by-products. However, certain metallic nanoparticles may risk accumulation

in tissues, raising long-term toxicity concerns.^{155,156} Additionally, the body's defense mechanisms, particularly the reticuloendothelial system (RES), can recognize and clear these nanoparticles, diminishing their therapeutic effectiveness. Modifications such as polyethylene glycol (PEG) can help extend circulation time in the bloodstream.

Moreover, some nanoparticles, especially those made from inorganic materials like gold or silver, can activate the immune system, leading to inflammation and rapid clearance from the bloodstream. This immune response can reduce the nanoparticles' therapeutic effectiveness and, in some cases, trigger the generation of antibodies, complicating repeated treatments. Certain nanoparticles may also exhibit cytotoxicity due to their material composition or interactions with biological systems, such as generating reactive oxygen species (ROS), which can cause oxidative stress and cellular damage. These potential risks, including immune responses and toxicity, must be carefully evaluated through preclinical and clinical studies to ensure the safety and effectiveness of nanoparticle-based therapies.

4.2 Efficiency and specificity of drug delivery

Achieving efficient and specific delivery to tumor cells remains a major challenge for nanoparticle systems. Despite the enhanced permeability and retention (EPR) effect that allows nanoparticles to accumulate in tumors, this process is not always consistent or efficient across different tumor types, including ESCC. Tumor heterogeneity, variations in vascular permeability, and the presence of biological barriers, such as



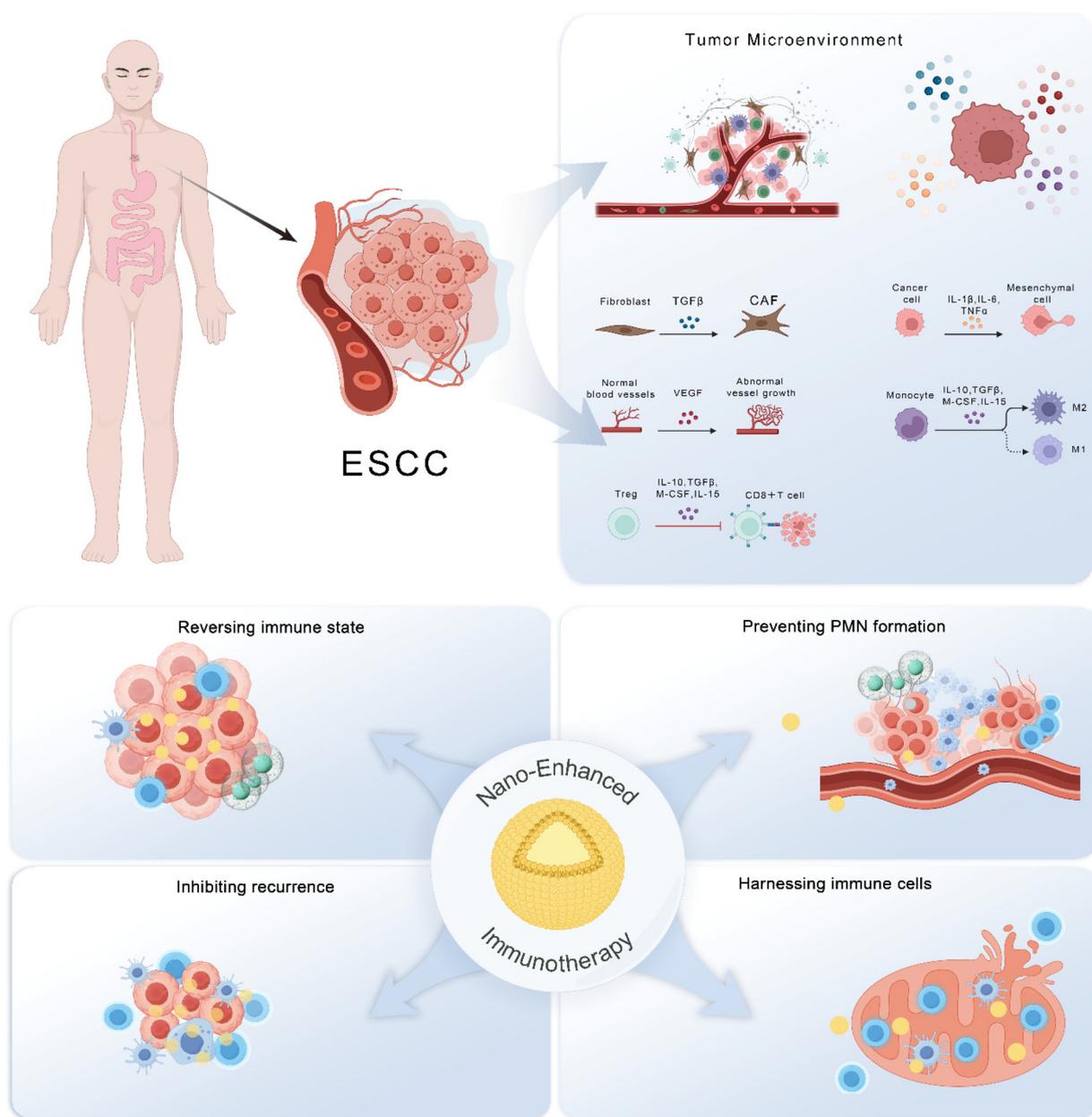


Fig. 5 Immune microenvironment of ESCC and the mechanisms of nanoparticle-mediated immunotherapy.

dense extracellular matrices, can limit the penetration of nanoparticles into the tumor tissue.¹⁵⁷ Additionally, nanoparticles need to be precisely targeted to cancer cells to avoid uptake by healthy tissues, which could lead to off-target effects and toxicity.¹⁵⁸

4.3 Manufacturing and scalability

The development of nanoparticle drug delivery systems involves complex manufacturing processes that are crucial for their clinical application. While the quest for clinically effective treatments for esophageal squamous cell carcinoma (ESCC) continues, advancements in nanotechnology have enabled the exploration of various production methods.^{159,160}

Large-scale production techniques such as lipid nanoparticles (LNPs) and liposomes are well-established, offering scalable solutions for drug delivery systems.¹⁶¹ Recent breakthroughs in the amplification of extracellular vesicles have contributed to the field, providing novel approaches to nanoparticle production.¹⁶¹ These advancements offer potential for scalable and cost-effective production methods, which are crucial for translating nanotechnologies into clinically viable treatments.¹⁶² The focus is on developing methods that ensure consistent quality, safety, and efficacy, which are paramount for regulatory approval and public health protection.¹⁶³

In summary, the scalability of nanoparticle production is driven by the need for innovative and efficient manufacturing



processes that can meet the demands of various therapeutic applications. The progress in this field is based on existing facts and advancements in technology, rather than being limited to the clinical outcomes of specific diseases.^{163,164}

The complex immune microenvironment of esophageal squamous cell carcinoma (ESCC), which is characterized by immune suppression, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs). Nanoparticle-based drug delivery systems are depicted as reversing immune state, preventing PMN formation, inhibiting recurrence and harnessing immune cells. Partly created with biorender.com.

4.4 Ethical challenges

Nanoparticle therapies present ethical concerns, primarily regarding long-term health and environmental impacts, and ensuring equitable access to these treatments.¹⁶⁴ Transparency about potential risks and benefits is essential to maintain public trust and informed consent. Ethical use and regulatory oversight are vital to prevent misuse and protect public health.

5. Future prospects

The future of nanoparticle-based drug delivery for ESCC treatment is promising, with advancements in nanotechnology and cancer biology offering solutions to current challenges. Novel, biocompatible nanomaterials, including hybrid and “smart” nanoparticles, are being developed for better stability, targeting, and controlled drug release, with the ability to respond to tumor-specific stimuli.

Given the advanced stage at which ESCC is often diagnosed, targeting the tumor microenvironment is crucial. Nanoparticles can be engineered to target biomarkers like PD-L1, enhance immune responses, and inhibit tumor migration, reshaping the immune-suppressive microenvironment for improved outcomes such as PD-L1, enhancing immune responses and inhibiting tumor cell migration.^{165,166}

Personalized nanomedicine, tailored to each patient's tumor profile, is another exciting direction.^{15,167} Advances in genomics will enable the design of nanoparticles that target specific genetic alterations, improving treatment efficacy and reducing side effects.¹⁶⁸

Emerging therapies like photodynamic and photothermal therapy, combined with nanoparticle delivery, offer additional strategies to treat ESCC by inducing targeted cell damage, providing new options for challenging cases.¹⁶⁹

6. Conclusions

Nanoparticle-based drug delivery systems represent a transformative approach for treating ESCC. By enhancing drug targeting and delivery, these systems can improve therapeutic outcomes while minimizing side effects. However, significant challenges such as biocompatibility, targeted delivery, and

regulatory hurdles must be addressed to facilitate clinical adoption. Continued research and innovation in this field will be essential for unlocking the full potential of nanoparticles in cancer therapy.

Author contributions

Linjia Peng and Yanfeng Liang conceptualized the article and were responsible for drafting the manuscript and data analysis. Zixuan Gao, Qiuli Zhang, and Xiaonan Guo contributed to the writing of specific sections and conducted a thorough review and revision of the manuscript. Daxiang Cui reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

Data availability

Permission has been acquired for the use of all figures' copyright in this review.

This is a review paper. No primary research results, software or code have been included and no new data were generated or analysed as part of this review. This review cited some data from published papers, and matched data can be obtained from the matched published papers.

Conflicts of interest

All authors declare no conflict of interest.

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