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Review Article

Current Status and Future Prospect of Receptor Targeted Nanocarrier Delivery of Cancer Therapeutics

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ABSTRACT

Cancer is an intricate and prevalent disease affecting millions of people worldwide. While conventional treatments like radiation therapy and chemotherapy remain standard approaches, they often come with severe side effects and unintentional damage to healthy cells. In response to these challenges, targeted drug delivery systems have developed as a promising strategy in cancer therapy. These systems offer the benefit of targeting drug delivery specifically to cancer cells, mitigating toxicity to surrounding normal tissues and enhancing treatment efficacy. This review provides a comprehensive analysis of the current landscape of targeted drug delivery systems in cancer treatment. It explores the different types of these systems, their mechanisms, and associated challenges, such as drug resistance, stability, and scalability. Additionally, recent advancements in nanotechnology, receptor-targeted approaches, and stimuli-responsive drug delivery methods will be discussed, highlighting their potential to improve precision in cancer treatment. Furthermore, this review examines future research directions, including the integration of artificial intelligence in drug design, the advancement of versatile nanocarriers, and the incorporation of immunotherapeutic agents. By assessing both the progress and potential of targeted drug delivery systems, the objective of this review is to underscore their significance in revolutionizing cancer therapy. Ultimately, these innovations hold the potential of enhancing treatment outcomes, mitigating side effects, and enhancing the well-being of individuals living with cancer.

Keywords: Receptor-mediated targeting, Nanocarriers, Personalized cancer therapy, Stimuli-responsive nanoparticles.

INTRODUCTION

Cancer is a complicated group of disorders marked by unfettered cellular proliferation and the capacity for invasion or dissemination to other body regions, referred to as metastasis.[1,2] It is not a single disease but comprises approximately 200 varieties, including carcinomas, sarcomas, leukemias, and lymphomas, categorized according to the tissue or organ of origin. The pathogenesis of cancer encompasses genetic alterations, which may be inherited or acquired, with environmental variables like tobacco smoke, radiation, and infectious agents such as HPV and hepatitis viruses.[3,4] By 2050, global cancer cases are anticipated to surpass 35 million, representing a 77% increase over the assessed 20 million cases in 2022. That year, cancer incidence worldwide led to over 9.7 million deaths, making it the second most common reason for mortality in economically developed nations.[5] To mitigate the progress of cancer, a significant effort has been made to improve the efficacy of cancer management strategies. Cancer therapies have evolved significantly over time, encompassing various approaches such as surgery, radiation, chemotherapy, and immunotherapy. While surgery and radiotherapy are primarily used for early-stage, localized, non-metastatic cancers, chemotherapy and immunotherapy are typically employed for cancers that are resilient to radiation or surgery, as well as those with metastases.[6-8] Although highly effective at destroying cancer cells, chemotherapy lacks precision, leading to drug-induced damage in healthy tissues.[9] Patients undergoing non-specific cancer treatments often suffer from intense adverse effects, including immune suppression, organ toxicity, and secondary malignancies. These treatments also induce drug resistance through genetic and epigenetic changes, reducing long-term efficacy. Additionally, they fail to address cancer heterogeneity, where cells within the same cancer respond differently, and limit overall effectiveness.[10-12] Nanocarrier drug delivery systems provide notable benefits over traditional non-specific cancer treatments by enhancing therapeutic efficacy and mitigating systemic toxicity. These carriers, including polymeric nanoparticles, nanocrystals, and protein-based systems, facilitate targeted drug transport to cancer cells while preserving healthy tissues.[13-15] Their enhanced permeability and retention (EPR) effect promotes greater cancer accumulation, leading to improved drug bioavailability and reduced dosage needs.[13,16]

Although nanocarrier drug delivery systems have many advantages it has some limitations in terms of specificity and pharmacokinetic parameters. Convectional nanocarriers have a lack of specificity, which often results in the non-specific distribution of drugs, leading to injury to unaffected tissues and severe side effects. This is particularly problematic in chemotherapy, where the cytotoxic effects are not restricted to cancer cells, causing toxicity and increasing the risk of developing drug resistance.[17-19] Conventional formulations also experience low bioavailability and stability within the cancer microenvironment, which limits their therapeutic efficacy.[19,20] In contrast, targeted drug delivery systems, particularly those utilizing nanotechnology, offer enhanced specificity by concentrating therapeutic agents within cancer while reducing systemic exposure. This is achieved through mechanisms such as ligand-NP conjugation, which allows nanoparticles to selectively bind to cancer-specific markers, thereby improving drug efficacy and minimizing off-target effects.[15,17] Active targeting involves surface modifications of nanoparticles to interact with specific receptors or antigens overexpressed in cancer cells, enhancing drug delivery precision [21,22]. Fig. 1 illustrates functionalized nanocarriers specifically targeted to cancer cells through receptor-ligand interactions, enhancing site-specific drug delivery and therapeutic efficacy. Furthermore, targeted systems can provide sustained and controlled drug release, improving the pharmacokinetic and pharmacodynamic profiles of anticancer drugs.[23]

Recent reviews have explored the role of various nanocarriers as nanomedicines in cancer research. This discussion provides a concise overview of key factors in designing targeted nanocarriers, highlights commonly used ligands, and summarizes recent advancements in the field.

Nanocarriers for Targeted Delivery

Nanocarriers are colloidal nanoscale systems designed to transport anticancer agents, including small molecular weight drugs or macromolecules such as genes or proteins. This indirect method of targeted therapy enables these agents to evade normal tissues and accumulate in cancerous cells, achieving a cytotoxic concentration significantly higher in the cancerous cells while minimizing toxicity to the surrounding healthy tissues compared to free drugs.[24] To date, numerous nanoformulations have been approved for clinical use in cancer chemotherapy, with several nanomedicines currently undergoing clinical trials (Table 1). To further harness the benefits of nanocarriers, researchers have been actively developing functionalized nanocarriers by modifying their surfaces with targeting ligands to increase their accumulation in cancerous tissues [25] and endowing NDDSs with specific responsiveness for drug release [26], enzymes [27], glutathione (GSH) [28] and temperature [29] *via in-vivo* as well as *in-vitro* stimulation. Multifunctional NDDSs hold great potential in addressing challenges related to low drug delivery efficiency and inadequate anticancer efficacy, particularly in the treatment of

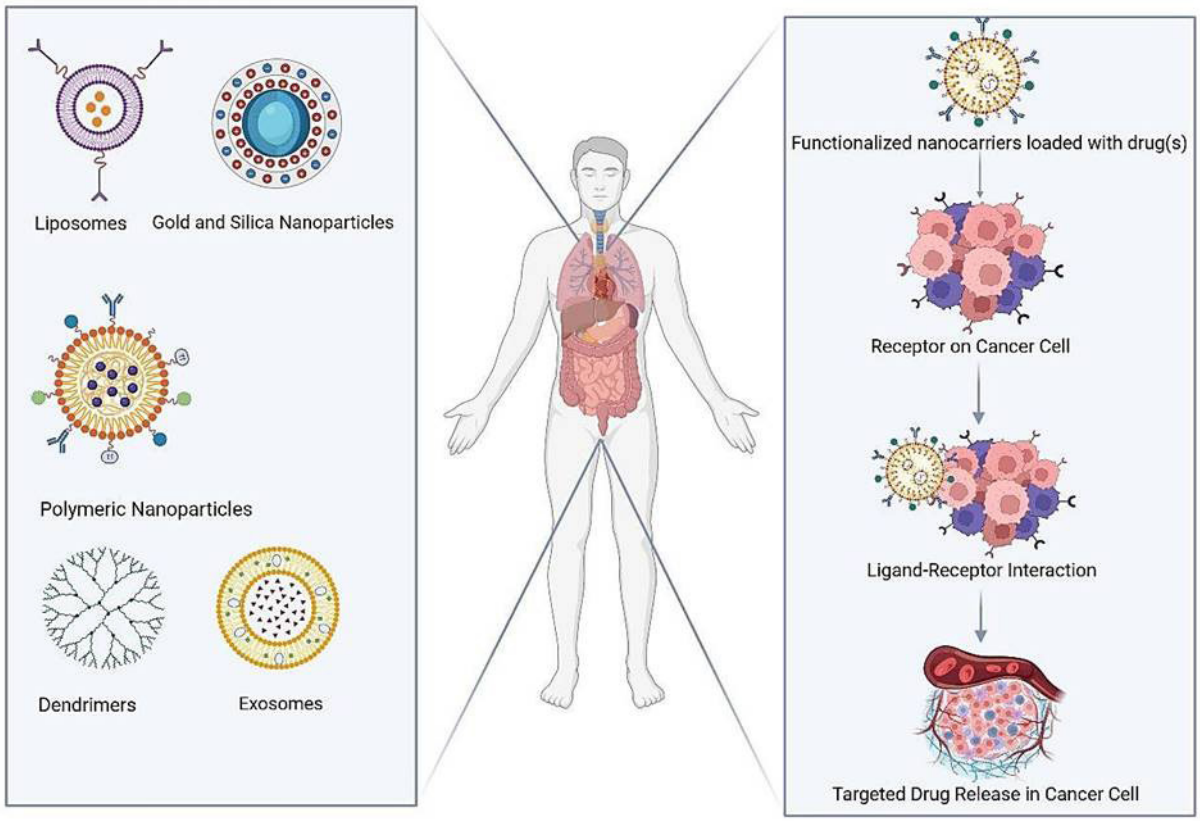

Fig. 1: Schematic representation of functionalized nanocarriers targeted to cancer-specific receptors. The nanocarriers are surface-modified with targeting ligands (e.g., antibodies, peptides, or aptamers) that recognize and bind to overexpressed receptors on cancer cells, enabling receptor-mediated endocytosis and localized drug release (Created in https://BioRender.com).

multidrug-resistant (MDR) cancers. The schematic diagram illustrating the "Current Status and Future Prospect for Drug Delivery System" is presented in Fig. 2, highlighting the evolution from conventional receptor-targeted nanocarriers to advanced, personalized, and AI-integrated therapeutic strategies. These advancements pave the way for the clinical application of NDDSs. Additionally, due to the constraints of single-agent chemotherapy, combination therapy strategies leveraging NDDSs are gaining prominence [30,31].

Liposomes

Liposomes are nanoscale vesicles made up of phospholipid bilayers, which have emerged as a revolutionary tool in cancer therapy. Their capability to encapsulate both water-soluble and fat-soluble drugs, combined with their biocompatibility and capability to target specific tissues, makes them an ideal platform for cancer treatment. Their structural versatility allows them to encapsulate a broad range of therapeutic agents, such as chemotherapeutics, genes, and diagnostic

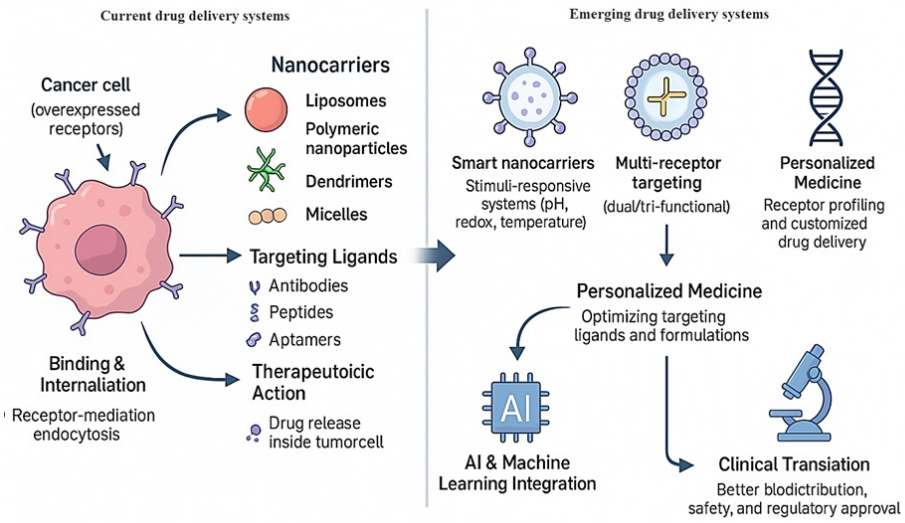

Fig. 2: Schematic representation of current and emerging drug delivery systems for cancer treatment. Present approaches focus on conventional chemotherapy, targeted therapies, and nanoparticle-based systems, while future strategies aim to integrate personalized medicine, smart nanocarriers, stimuli-responsive systems, and AI-guided delivery platforms for enhanced specificity, efficacy, and reduced side effects.

Table 1: Targeted NDDSs currently in clinical trials

Product name	*Drug(s)*	*Target*	*Disease*	*Nanocarrier type*	*Phase*	*Company*	*Reference*
Lipoplatin	Cisplatin	Cancer cells	Non-small cell lung cancer (NSCLC)	Liposomal nanoparticle	Phase III completed	Regulon Inc.	[32]
NK012	SN-38 (irinotecan metabolite)	Cancer cells	Relapsed small-cell lung cancer and triple-negative breast cancer	Polymeric micelle	Phase II completed	Nippon Kayaku Co.	[33]
CRLX101	Camptothecin	Cancer cells	Advanced solid cancers	Cyclodextrin-based polymer conjugate	Phase I/IIa completed	Cerulean Pharma Inc.	[34]
EndoTAG-1	Paclitaxel	Cancer vasculature	Pancreatic Adenocarcinoma	Cationic liposome	Phase III ongoing	Medigene AG	[35]
Paclitaxel trevatide (NG1005)	Paclitaxel-Angiopep-2 conjugate	Blood-brain barrier and cancer cells	Various CNS cancers including glioma	Peptide-drug conjugate	Preparing for Phase III	Angiochem Inc.	[36]
Rhenium (186Re) Obisbemeda	Rhenium-186 radiolabeled therapeutic	Cancer cells	Recurrent Glioblastoma, Leptomeningeal Metastases, Pediatric Brain Cancers	Nanoliposome-encapsulated radiotherapeutic	Phase I ongoing	Plus Therapeutics	[37]
Doxorubicin	Doxorubicin	MRP1 mRNA	Lung cancer	Liposomal delivery system	Preclinical	Not specified	[38]
Inpg	Drug polymer conjugate	Cancer cells	Metastatic breast cancer	Injectable nanoparticle generator	Preclinical	Not specified	[8]

multidrug-resistant (MDR) cancers. The schematic diagram illustrating the "Current Status and Future Prospect for Drug Delivery System" is presented in Fig. 2, highlighting the evolution from conventional receptor-targeted nanocarriers to advanced, personalized, and AI-integrated therapeutic strategies. These advancements pave the way for the clinical application of NDDSs. Additionally, due to the constraints of single-agent chemotherapy, combination therapy strategies leveraging NDDSs are gaining prominence.[30,31]

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Polymeric nanoparticles

Polymeric nanoparticles have emerged as a promising receptor-targeted delivery system for cancer treatment, offering significant advantages over conventional therapies by enhancing drug delivery specificity and reducing systemic toxicity. These nanoparticles are designed to improve the pharmacokinetics and bioavailability of anticancer drugs, facilitating targeted accumulation at specific sites through mechanisms like the EPR effect and ligand-mediated active targeting.[48,49] The use of pH-sensitive polymeric nanoparticles, for example, those made from chitosan and poly(lactic-co-glycolic acid) (PLGA), is particularly effective in targeting the acidic cancer microenvironment, thereby improving drug release and reducing side effects on normal tissues.[50] In breast cancer, polymeric nanoparticles can be chemically grafted with polymers and surface modifiers to target specific receptors, such as HER2, allowing for controlled drug release and high selectivity, which results in better accumulation inside cancer cells while protecting normal cells.[51] Furthermore, protein-based nanocarriers, which utilize targeted ligands like antibodies and amino acids, offer another layer of specificity by ensuring that medications specifically concentrate within cancer cells, thus minimizing systemic toxicity.[52] Despite advancements, challenges still exist, including scaling up production, maintaining long-term biocompatibility, and navigating regulatory obstacles.[15,50] However, ongoing research and development in multifunctional nanoparticles and personalized treatments tailored to individual patients hold promise for significantly improving cancer treatment outcomes.[50,53] The combination of nanotechnology with other treatments, like immunotherapy and radiation therapy, further underscores the potential of polymeric nanoparticles to revolutionize cancer treatment by enhancing precision and reducing adverse effects.[54]

Dendrimers

Dendrimers have a unique structural property, which includes a highly branched, three-dimensional architecture that allows for

Table 2: Summary of approved liposomal formulations for cancer treatment [47]

Product name	*Manufacturing company*	*Drug*	*Liposome materials*	*Targeted disease*
Doxil®	Sequins Pharma	Pegylated liposomal doxorubicin	Lecithin N-[carbonylmethoxy polyethylene glycol 2000]-1,2-stearoylsn-glycerol-3-phosphoethanolamine sodium salt (MPEG-DSPE), cholesterol, hydrogenated soy phosphatidylcholine (HSPC)	Metastatic extraovarian primary peritoneal carcinoma, myelodysplastic syndrome, and Kaposi's cancer with advanced HIV infection
DaunoXome®	Nexstar Pharma	Daunorubicin	Di-stearoyl phosphatidylcholine, triglycerides	Kaposi's sarcoma
Depocyt®	SkyePharm Inc.	Aracytidine	Sterol, Glyceryl trioleate, di-oleoyl phosphatidylcholine (DOPC), and dipalmitoyl phosphatidylglycerol (DPPG)	Neoplasia meningitis
Myocet	Elen Pharma, New Jersey, USA	Daunorubicin	Cholesterol, egg phosphatidylcholine	Metastatic breast cancer
Mepact®	Takeda Pharma Limited,	Mifamurtide	Muramyl tripeptide phosphatidylethanolamine	Non-metastatic bone cancer
Marqibo®	Talon Pharma, Inc., US	Vincristine	Sphingomyelin, cholesterol	Refractory cancer

precise functionalization and drug encapsulation. These nanoscale molecules can be tailored to enhance the targeted delivery of drug(s) specifically to cancer cells, thereby minimizing systemic toxicity and improving therapeutic outcomes.[55,56] For instance, dendrimers can be conjugated with specific targeting molecules, such as antibodies or ligands, to improve the specificity of drug(s) delivery to cancer cells, as demonstrated in the development of a PSMA-targeted dendrimer for prostate cancer, which showed selective uptake in PSMA-positive cells and reduced systemic side effects.[57] Additionally, dendrimers can be used in combination with metal-phenolic networks to deliver antibodies and other therapeutic agents, as seen in the DPGMA platform, which integrates chemotherapy, chemodynamic therapy, and immune checkpoint blockade for enhanced cancer inhibition.[58] The versatility of dendrimers also extends to their use in combinatorial therapies, where they can carry multiple drugs simultaneously, reducing the required dosage and associated side effects while overcoming multidrug resistance.[59] Furthermore, dendrimers have been shown to improve drug solubility and bioavailability, addressing common challenges in cancer treatment, such as non-specific toxicity and poor drug solubility.[60] Despite these challenges like scalability, biocompatibility, and cancer heterogeneity persist, requiring further research in dendrimer-based drug delivery.[15,61] Overall, the continued development of dendrimer technology holds significant potential for improving the effectiveness and specificity of cancer therapies, potentially transforming the landscape of oncological treatment.[62]

Gold and silica nanoparticles

Gold and silica nanoparticles have offered significant advantages regarding specificity, efficacy, and reduced systemic toxicity. Gold nanoparticles, known for their optical and thermo-plasmonic properties, can be integrated into multifunctional nanostructures that combine photothermal therapy, photodynamic therapy, and chemotherapy, as demonstrated by the RB-AuSiO2_HSA-DOX system, which utilizes a gold core and silica shell to improve drug delivery and targeting capabilities.[63] Silica nanoparticles, particularly mesoporous silica nanoparticles (MSNs), are recognized for their high drug-loading capacity and controlled release, which improve drug permeability and retention while minimizing adverse effects on healthy.These nanoparticles can be designed to selectively bind to specific cancer cell receptors through surface modifications, enabling precise drug delivery and enhancing therapeutic outcomes cells.[64,65] Incorporating stimuli-responsive systems that release drugs based on environmental changes like pH or temperature further improves the targeting ability of these nanoparticles.[53,61] Additionally, the use of protein-based nanocarriers, which can be conjugated with ligands to target surface receptors, offers another layer of specificity and safety, reducing systemic toxicity and improving drug accumulation in cancer cells.[52] Although there have been promising advancements, challenges such as immune system evasion, scalability, and cancer heterogeneity remain, necessitating further research and innovation to optimize these systems for clinical application.[54,61] Overall, gold and silica nanoparticles represent a transformative approach to cancer treatment, having the capability to transform targeted drug delivery and improve patient outcomes through personalized and multimodal therapies.[48,54]

Exosomes

Exosomes, as nanoscale extracellular vesicles, offer low immunogenicity, high biocompatibility, and the ability to efficiently target cancer cells, making them ideal candidates for drug delivery vehicles in cancer treatment.[66,67] These vesicles can be designed to carry therapeutic agents, such as small interfering RNAs (siRNAs), chemotherapeutic drugs, and other molecular therapies, directly to cancer sites, thereby improving drug stability and minimizing systemic toxicity.[67,68] For instance, exosome-mediated delivery of siRNAs has shown promise in targeting cancer-associated genes, with some formulations advancing through clinical trials.[67] Additionally, dual-targeting strategies, such as combining exosomes with iron oxide crystals coated in carbohydrate nanoparticles, have been developed to enhance the accuracy of drug delivery, as demonstrated in non-small cell lung cancer models where this approach improved cancer suppression and reduced normal tissue toxicity.[69] The integration of exosomes with other nanomaterials, such as magnetic nanoparticles, further enhances their targeting capabilities and therapeutic efficacy, as seen in ovarian cancer therapy, where exosomes were used to deliver a combination of miRNA and chemotherapeutic agents.[70] Although these advancements remain, challenges remain, including the standardization of exosome production and the need for further research to fully understand their biological mechanisms and optimize their clinical application.[66,71] Overall, exosome-driven drug delivery systems hold significant potential for transforming cancer treatment by providing targeted, efficient, and less toxic therapeutic options.[72,73]

Receptor Targets for Cancer Therapy

Folate Receptor

Folate receptors (FRs) have emerged as promising targets for cancer therapy due to their over-expression in various cancer types, including ovarian, breast, and oral cancers while being inadequately expressed in normal tissues. This differential expression makes FRs ideal for targeted drug delivery systems, enhancing therapeutic efficacy and minimizing systemic toxicity. Several studies have investigated the application of folate-conjugated nanocarriers for delivering chemotherapeutic agents. For instance, folate-targeted liposomal bleomycin has shown increased effectiveness in reducing cell viability and inducing cell cycle interruption in FR-overexpressing cancer cells compared to non-targeted formulations, highlighting the potential of folate-mediated targeting in reducing side effects and improving drug delivery.[74] Similarly, folate receptor-targeted nanoparticles have been designed for the delivery of apigenin and combination therapies like paclitaxel and curcumin, demonstrating enhanced cytotoxicity and cancer specificity in breast cancer models.[75,76] Additionally, folate receptor-targeting chimeras have been designed to degrade extracellular proteins selectively in cancer cells, offering a novel approach to precision medicine.[77] Computational chemistry has further advanced the design of folate-based anticancer drugs by providing insights into drug-receptor interactions, which are crucial for enhancing binding affinities and specificity.[78] Folate receptor alpha (FRα) is particularly significant in cancer therapy, being utilized in antibody-drug conjugates and chimeric antigen receptor T cells (CAR-T cells), with ongoing clinical trials exploring

its potential.[79] Moreover, folate-targeted photodynamic therapy has demonstrated potential in stimulating anticancer immune responses, particularly in ovarian cancer, by promoting immune cell activation and cytokine modulation.[80] These advancements underscore the versatility and potential of folate receptor-targeted therapies in improving cancer treatment outcomes across various modalities, including drug delivery, protein degradation, and immunotherapy.[81]

Epidermal growth factor receptor

Epidermal growth factor receptor (EGFR) is a critical target in cancer therapy due to its role in cellular signaling pathways that drive cancer growth and progression. Various strategies have been designed to target EGFR, such as tyrosine kinase inhibitors (TKIs), monoclonal antibodies, and novel approaches like protease-targeted chimeras (PROTACs) and peptide vaccines. TKIs and monoclonal antibodies have demonstrated effectiveness in treating cancers like non-small cell lung cancer (NSCLC), colorectal cancer, and glioblastoma, but their effectiveness is often limited by drug resistance and cancer heterogeneity.[82-84] To address these challenges, dual-target inhibitors and PROTACs have been developed, offering improved efficacy and reduced resistance by targeting multiple pathways or promoting protein degradation.[84,85] Additionally, precision medicine approaches, such as the use of biomarkers for patient stratification and the development of neoantigen peptide vaccines, have demonstrated the potential to improve the specificity and effectiveness of EGFR-targeted therapies.[86,87] These vaccines, particularly those targeting EGFR mutations like EGFRvIII, have demonstrated safety and efficacy in clinical trials, suggesting a potential for combination with other therapies to boost anticancer responses.[87] Furthermore, the use of nanoparticles for targeted drug delivery is being explored to reduce unintended effects and enhance therapeutic outcomes.[88] Although these advancements, challenges persist, particularly in addressing kinase-independent functions of EGFR and its nuclear localization, which contribute to therapeutic resistance.[83,89] Overall, the integration of these diverse strategies into a comprehensive treatment regimen holds promise for improving outcomes in EGFR-driven cancers, underscoring the importance of continued research and innovation in this field.[90]

Transferrin receptor

The transferrin receptor (TfR) is a carrier protein for transferrin has appeared as a potential target for cancer therapy due to its over-expression in various cancer types, facilitating the delivery of therapeutic agents directly to cancer cells. Transferrin receptor targeting chimeras (TransTACs) have been designed to exploit this receptor for targeted degradation of membrane and extracellular proteins, offering a novel approach to treat drug-resistant cancers such as EGFR-driven lung cancer and to control CAR-T cells.[91,92] Additionally, transferrin-modified nanoparticles, such as Fe3O4 NPs, have been used to deliver miR-15a-5p in conjugation with photothermal therapy, demonstrating enhanced inhibition of lung cancer cell growth by targeting the TfR.[93] Peptide-drug conjugates (PDCs) like DT7-SS-DOX, which utilize TfR-targeting peptides, have shown improved selectivity and stability in delivering doxorubicin to cancer cells, reducing toxicity to normal cells.[94] In breast cancer, TfR expression is prevalent across various stages and subtypes, and its modulation can enhance the uptake of therapeutics, suggesting that TfR-targeted strategies could be customized for each patient profile.[95] Furthermore, TfR-targeted nanomedicines have been designed to cross the blood-brain barrier (BBB), offering the potential for brain cancer therapy by utilizing the receptor's ability to mediate transcytosis.[96] Liposomal drug delivery systems targeting TfR have also been explored, highlighting the receptor's role in improving the efficacy and specificity of cancer treatments.[97] For cancer therapy, these diverse strategies underscore the versatility of TfR as a target, providing a foundation for developing more effective and personalized therapeutic approaches.

Hyaluronic acid receptor

Hyaluronic acid (HA) interacts with cell surface receptors, mainly CD44 and (RHAMM) receptor for hyaluronic acid-mediated motility, playing a significant role in regulating cell movement, growth, and numerous biological functions such as inflammation and cancer progression. CD44, a transmembrane glycoprotein, acts as a key marker for cancer stem cells and is significantly overexpressed in multiple cancer types, including breast cancer, neuroblastoma, and neuroglioma.[98-100] The association between CD44 and HA facilitates targeted drug delivery, enhancing the accumulation of therapeutic agents at cancer sites and improving treatment efficacy.[101,102] HA's biocompatibility and modifiability make it an ideal candidate for creating drug delivery systems, such as HA-coated polymeric nanoparticles (PNPs) and nanocarriers, which leverage the EPR effect for selective cancer targeting.[103,104] These HA-based systems can be designed to react to distinct signals present within the cancer microenvironment, allowing for controlled drug release and minimizing systemic side effects. Additionally, HA's ability to bind to CD44 can be exploited to overcome multidrug resistance (MDR) mechanisms in cancer cells, thus improving the effectiveness of chemotherapy drugs.[103] However, the dual role of the HA/CD44 axis in cancer progression, where it can both promote and inhibit cancer growth, adds complexity to its therapeutic application.[105] The variability in CD44 expression and the potential for HA to modulate CD44-mediated signaling pathways necessitate careful consideration in the design of HA-based therapies.[105,106] Despite these constraints, the development of HA-functionalized nanocarriers and hydrogels continues to show promise in advancing targeted cancer therapies, offering the potential for more personalized and effective treatment regimens.[106]

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) has emerged as a pivotal target for cancer therapy, particularly in the milieu of prostate cancer, due to its high expression in malignant prostate tissues compared to normal tissues.[107,108] SMA-targeted therapies have been developed across various modalities, including antibody-drug conjugates (ADCs), radioligand therapies, and photo theranostics, each offering unique advantages and challenges.[109-111] ADCs, which selectively target PSMA-positive cancer cells, have shown promising anticancer activity and manageable toxicity profiles in

initial clinical trials, although further investigation is needed to optimize their efficacy and safety.[109] Radioligand therapies, such as 177Lu-PSMA-617, have demonstrated significant clinical success and received FDA approval for treating castration-resistant metastatic prostate cancer, although they are associated with high costs and side effects.[110,112] The combination of PSMA-targeted radioligand therapy and imaging, known as theranostics, has enhanced the identification and treatment of advanced prostate cancer, enabling more personalized therapeutic approaches.[112] Moreover, near-infrared (NIR) fluorescence imaging and phototherapy have gained recognition as effective approaches, offering advantages like deep tissue penetration and minimal adverse effects. These qualities make them especially valuable for fluorescence-guided surgery and targeted photothermal or photodynamic therapy.[110,111] Beyond prostate cancer, PSMA expression in cancer neovasculature of non-prostatic cancers presents opportunities for vasculature-directed therapies, including radioligand therapy and CAR T-cell therapy.[113] Despite these advancements, challenges such as unintended harmful effects and the need for precise imaging and therapeutic strategies remain, necessitating ongoing research and clinical trials to enhance the translational potential of PSMA-targeted therapies.[111,114] Overall, remains a groundbreaking target with transformative potential in prostate cancer therapy, with ongoing efforts to refine and expand its applications across different therapeutic platforms.[115]

Key Advancements in Receptor-Targeted Nanocarrier Systems

receptor-targeted nanocarrier systems have emerged as a promising frontier in precision oncology, enabling selective delivery of therapeutic agents to tumor cells while minimizing systemic toxicity. Recent advancements have focused on three critical areas: the strategic selection of ligands to enhance targeting specificity, the design of nanocarriers with optimized physicochemical properties for efficient delivery, and the development of multifunctional platforms capable of simultaneous diagnosis, therapy, and controlled release. These innovations collectively aim to overcome biological barriers, improve drug accumulation at the tumor site, and enable personalized treatment approaches. To visually summarize these key advancements, refer to Fig. 3.

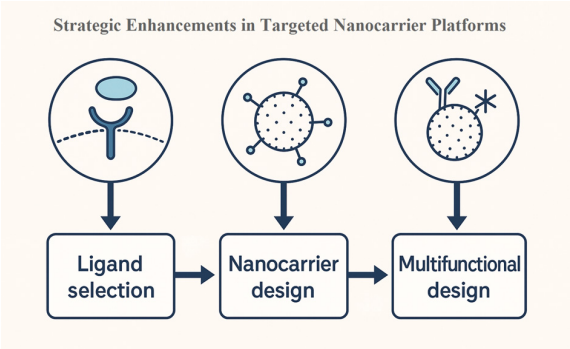

Fig. 3: Key advancements in receptor-targeted nanocarrier systems highlighting three pivotal areas: (1) Ligand selection for receptor-specific targeting, (2) Rational nanocarrier design for enhanced delivery efficiency, and (3) Multifunctional design enabling integrated diagnostic and therapeutic capabilities.

Ligand selection

The selection of ligands is primarily guided by the over-expression of specific receptors on cancer cells, such as the EGFR, which is frequently targeted using anti-EGFR ligands to facilitate receptor-mediated endocytosis and improve drug accumulation within cancers.[116] Protein-based nanocarriers, which utilize ligands like antibodies, amino acids, and vitamins, offer biodegradability and biocompatibility, reducing systemic toxicity and enhancing therapeutic efficacy by ensuring selective drug accumulation in cancer cells.[52] Various ligands, including small molecules, aptamers, peptides, and antibodies, have been discovered for their potential to target overexpressed receptors on cancer cells, with aptamers being particularly noted for their high affinity and specificity, comparable to monoclonal antibodies.[117,118] The use of dual-ligand systems, such as those targeting both CD44 and folate receptors, has shown promise in increasing targeting specificity and reducing unintended interactions, although challenges remain in optimizing ligand density for effective targeting.[119,120] RNA nanoparticles have also been employed, with ligands like methotrexate enhancing specific binding to overexpressed receptors, although care must be taken to balance ligand density to avoid adverse effects on nanoparticle stability and biodistribution.[121] Lipid-based nanocarriers further illustrate the importance of ligand selection, as they can be functionalized with specific ligands to achieve site-targeted drug delivery, addressing issues of poor drug absorption and bioavailability associated with conventional therapies.[122] Overall, the strategic selection and optimization of ligands in nanocarrier systems are pivotal for advancing cancer-targeted therapies, providing the possibility for greater customization and effective treatment options.[123,124]

Nanocarrier design

Nanocarrier design in receptor-targeted cancer therapy enhances treatment efficacy and specificity while mitigating systemic toxicity. Protein-based nanocarriers, for instance, leverage their biocompatibility and biodegradability to deliver drugs directly to cancer cells by targeting surface receptors, thereby minimizing off-target effects and systemic toxicity.[52] The functionalization of nanocarriers with ligands such as anti-EGFR molecules exemplifies active targeting, which is more specific than passive targeting, as it facilitates receptor-mediated endocytosis and improves drug accumulation in cancers.[116] Advances in nanotechnology have enabled the development of various nanocarrier systems, such as liposomal vesicles, dendritic polymers, and polymer-based nanoparticles, that employ both passive and active targeting mechanisms to concentrate drugs within cancers.[15] These systems are further enhanced by stimuli-responsive features that allow for controlled drug release in response to environmental changes like pH and temperature.[61] The integration of nanocarriers with immunotherapy and other treatment modalities, such as radiation therapy, has shown potential to improve therapeutic outcomes and overcome multidrug resistance by targeting the cancer microenvironment.[54,125] Although substantial advancements have been achieved, obstacles like immune system evasion, scalability issues, and the complication of cancer heterogeneity remain. Continuous research is crucial for optimizing nanocarrier design and enhancing their safety and effectiveness for clinical use.[61] Overall,

the continued development of receptor-targeted nanocarrier systems holds promise for more personalized and effective cancer therapies, potentially revolutionizing patient outcomes in oncology.[53,54]

Multifunctional design

Multifunctional nanocarrier systems, including nanocarriers composed of organic (liposomes, micelles, dendrimers) or inorganic (gold nanoparticles, quantum dots, SPIONs) materials, are engineered with targeting ligands like peptides or antibodies to recognize specific receptors overexpressed on cancer cells, enabling precise drug delivery [126]. Moreover, the integration of imaging agents enables real-time monitoring, while stimuli-responsive elements allow controlled drug release triggered by cancer-specific conditions like pH, enzymes, or temperature [127]. Recent advances in magnetic nanocarriers and protein-based nanoplatforms have demonstrated enhanced targeting and therapeutic potential, though challenges such as biocompatibility, large-scale manufacturing, and regulatory hurdles remain [128]. Addressing these issues through innovative design strategies and personalized medicine approaches could lead to the development of more effective clinical applications of multifunctional nanocarriers in cancer treatment.

Major challenges in receptor-targeted nanocarrier delivery systems

Cancer heterogeneity

Cancer heterogeneity is evident both between different cancers and within a single cancer, affecting the expression of target receptors and the cancer microenvironment, which in turn influences the delivery and efficacy of nanomedicines [129,130]. The variability in receptor expression, such as the diverse isoforms and modifications of CD44, complicates the design of targeted therapies, as these variations can lead to inconsistent binding and uptake of nanocarriers [131]. Additionally, the cancer microenvironment, characterized by factors such as hypoxia and the presence of cancer-associated fibroblasts (CAFs), can act as physical and biochemical barriers to effective drug delivery [132]. These barriers necessitate the personalization of delivery systems to match the specific characteristics of each cancer, which is a complex and resource-intensive process [129]. Furthermore, the limited number of receptors that can be effectively targeted across various types of cancer restricts the applicability of receptor-targeted strategies [133]. Despite these challenges, advancements in nanotechnology, such as the advancement in smart drug delivery systems and combinatorial nanomedicines, offer promising avenues to enhance targeting specificity and therapeutic efficacy [17,134]. These systems can be designed to exploit the over-expression of specific receptors on cancer cells, using ligands, i.e., peptides, antibodies, and aptamers, to improve targeting accuracy [135]. However, the clinical translation of these technologies remains hampered by the challenge of translating laboratory research into practical applications, ensuring that these systems can effectively navigate the complex cancer landscape to deliver therapeutic agents precisely and efficiently [117,136].

Extracellular barriers

Extracellular barriers include the extracellular matrix (ECM), which can hinder drug penetration and accumulation, particularly in cancer environments. For instance, the dense hyaluronic acid (HA) in the cancer ECM acts as a physical barrier, reducing drug delivery efficiency. To address this, engineered nanocarriers such as c(RGDyK)-HAase-IONP have been designed to damage HA, thereby enhancing drug penetration and accumulation in cancers, as demonstrated by improved cancer-targeting and therapeutic efficacy in preclinical models [137]. Additionally, the BBB presents a formidable challenge for drug delivery to the CNS. Nanocarriers targeting the transferrin receptor (TfR) have shown promise in overcoming the BBB, facilitating drug delivery to glioblastoma cells by enhancing drug retention at the target site [138]. Multifunctional polymeric nanocarriers are also designed to prolong circulation time and selectively bind to target tissues, thereby overcoming extracellular barriers and improving drug delivery efficiency [139]. Furthermore, extracellular vesicles (EVs) and lipid-like nanocages are explored for their natural biocompatibility and ability to penetrate physiological barriers, offering a potential pathway for targeted drug delivery [140,141]. The integration of transporter-targeted strategies further improves the efficiency and specificity of nanocarrier systems by exploiting overexpressed transporters in pathological states, facilitating drug transfer across biological barriers such as the intestinal and BBB [142,143]. Overall, overcoming extracellular barriers through innovative nanocarrier designs and targeting strategies is crucial for improving the therapeutic efficacy of receptor-targeted drug delivery systems.

Immune response

Receptor-targeted nanocarrier delivery systems have demonstrated substantial potential in modulating immune responses, which is essential for improving the effectiveness of therapeutic interventions such as vaccines and cancer immunotherapies. The interplay between nanocarriers and the immune system is intricate, involving both innate and adaptive immune responses. Lipid nanoparticles (LNPs), for instance, can trigger innate immune responses through pattern-recognition receptors like toll-like receptors, leading to the stimulation of inflammatory pathways and cytokine production, which can sometimes result in adverse effects. However, the response of the adaptive immune system typically targets the protein expressed by the mRNA payload rather than the LNP components themselves [144]. Targeting specific immune cells, such as dendritic cells (DCs), is a potential approach for enhancing immune responses. For example, mannose-modified carbon nanotubes (M-MWCNTs) have been proven to efficiently target mannose receptors on macrophages and DCs, promoting antigen uptake and enhancing both humoral and cellular immune responses [145] . Similarly, hybrid nanoparticles that co-deliver antigens and TLR agonists can synergistically activate DCs, improving vaccine efficacy and inducing robust T-cell responses [146]. The use of polyphosphoester-based surfactants for noncovalent targeting of nanocarriers to DCs has also been confirmed to improve specific uptake while maintaining low protein adsorption, thus preserving the "stealth" properties of the Nanocarriers [147]. Furthermore, nanoparticles can be designed to target Fc receptors on DCs, enhancing antigen presentation and immune activation, which is particularly beneficial in cancer immunotherapy [148]. Although progress has been made, challenges remain, such as the potential for immune-mediated toxicity and the need for precise targeting

to avoid off-target effects [133,149]. Overall, receptor-targeted nanocarrier systems represent a versatile and promising approach to modulating immune responses, offering potential breakthroughs in the treatment of infectious diseases, cancer, and other immune-related conditions [146].

Drug resistance development

Drug resistance mechanisms, such as the over-expression of efflux transporters like P-glycoprotein (P-gp), alterations in the cancer microenvironment (TME), and the occurrence of cancer stem cells, significantly hinder the effectiveness of conventional therapies [150,151]. Nanocarrier systems present an effective approach to overcoming these challenges by improving drug solubility, stability, and targeted delivery, eventually improving treatment effectiveness while reducing overall toxicity [151,152]. These systems exploit the EPR effect to accumulate in cancer tissues, which is crucial for reducing off-target effects and improving drug efficacy [151]. Nevertheless, the advancement of receptor-targeted nanocarriers is fraught with challenges, including the identification of suitable receptors, ligand selection, and the conjugation chemistry required for effective targeting [153]. Additionally, the heterogeneity of cancers and the dynamic nature of the TME further complicate the delivery of therapeutics, necessitating the design of multifunctional and adaptive Nanocarriers [136,154]. Despite these hurdles, advancements in nanotechnology, such as the co-delivery of multiple agents and the incorporation of theragnostic platforms, show potential in addressing multidrug resistance (MDR) by enabling precise targeting and real-time monitoring of treatment efficacy [152,155]. Future studies should prioritize enhancing these systems to enhance their clinical translation, addressing issues such as nanoparticle stability, cancer microenvironment barriers, and regulatory challenges [152,156]. By continuing to innovate in the field of nanomedicine, it is possible to develop more effective receptor-targeted delivery systems that can overcome the barriers posed by drug resistance, ultimately improving cancer treatment outcomes [125,157].

FUTURE DIRECTIONS AND CONCLUSION

receptor-targeted nanocarriers are set to revolutionize precision cancer treatment by incorporating advanced design strategies and multifunctional capabilities. Dual-ligand systems will enhance targeting specificity by engaging multiple receptors, improving cancer accumulation and cellular uptake. Cancer microenvironment-responsive ligands will enable stimuli-triggered drug release, increasing treatment effectiveness while reducing overall toxicity. Computational ligand design, powered by artificial intelligence, will accelerate the discovery of high-affinity targeting moieties, optimizing nanocarrier performance. Therapeutic cocktails combining chemo-agents with siRNA or mRNA will enable synergistic treatment approaches, addressing drug resistance and enhancing cancer suppression. Diagnostic capabilities will be augmented by incorporating quantum dots or contrast agents for simultaneous imaging and therapy monitoring. Immunotherapy integration will further enhance therapeutic outcomes by leveraging nanocarriers for efficient immune modulation. The use of biodegradable smart materials will ensure biocompatibility and controlled degradation, reducing long-term toxicity. Targeting specific organelles, such as mitochondria or nucleus-directed delivery, will enhance the precision of intracellular drug action, maximizing therapeutic benefits. Additionally, 4D nanocarriers capable of adapting their morphology post-administration will provide dynamic, responsive drug delivery solutions, further refining cancer treatment strategies. These advancements collectively lay the foundation for a new era of intelligent, highly effective nanomedicine in oncology.

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