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REVIEW

Current Advances in Nanocarriers for Cancer Therapy

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Abstract: Nanocarriers have shown optimal therapeutic outcomes through their great potential for encapsulating and effectively delivering bioactive compounds into target cells by navigating a series of intracellular barriers. In this review, drug resistance and cell barriers impeding the drug delivery process have been discussed. Besides, the efficiency of nanocarriers, along with recent advances and novel strategies to overcome drug resistance, increase cell internalization, promote intracellular trafficking, target subcellular locations, and control drug release, has been reviewed. Different types of nanocarriers from the viewpoint of cancer treatment have been introduced, and their prospect as drug delivery vehicles for cancer therapy have been visualized. Hence, this review may contribute to developing nanocarriers for effective and precise drug delivery to a wide range of cells and intracellular targets.

Keywords: cancer, drug resistance, drug delivery system, nanotechnology, nanocarriers

Introduction

Cancer is a genetic disorder marked by the unregulated proliferation and spread of aberrant cells, which may be triggered by external elements such as tobacco, pathogens, poor nutrition, chemical agents, radiation, and internal factors. Most cancers arise from DNA alterations in proto-oncogenes or tumor-suppressor genes.[1] Cancer remains the second most common cause of death, highlighting the urgent need for ongoing research and development of innovative therapies and treatment strategies.[2] The mainstay of cancer therapy revolves around chemotherapy, surgery, radiation therapy, and their combinations.[3] However, radiation causes acute radiation damage, including skin irritation and adverse effects on adjacent healthy tissues, and tissue-specific stem cells and tumor removal could prove fatal.[2] Chemotherapeutics may eliminate rapidly proliferating malignant cells; they may damage normal, fast-dividing cells, including those in the bone marrow, gastrointestinal tract, and hair follicles. The harmful effects of chemotherapy include direct toxicity and indirect toxicity, mediated by liver metabolites, systemic immune suppression, decreased oxygen delivery, and enhanced inflammation.[4] Consequently, creative options must be used to provide safer and more targeted cancer therapeutics.[4,5] Nanotechnology-based drug delivery systems (DDS) can optimize the delivery process by enhancing drug solubility, blood circulation, and tumor site accumulation, while reducing therapeutic interactions and facilitating controlled release.[6] The application of nanotechnology in cancer treatment has shown significant progress in terms of negating the adverse effects like neurotoxicity and tissue damage.[7] Nanoparticles (NPs) (particles less than 100 nm in size) have made a profound impact on DDS by shielding drugs from degradation, delivering them precisely to the intended targets, and regulating their release.[8] There has been a significant improvement in NP delivery strategy, including efficacy, stability, safety, and the pharmacokinetic profile of the NPs used for chemotherapeutic purposes.[9] Cancer-targeting

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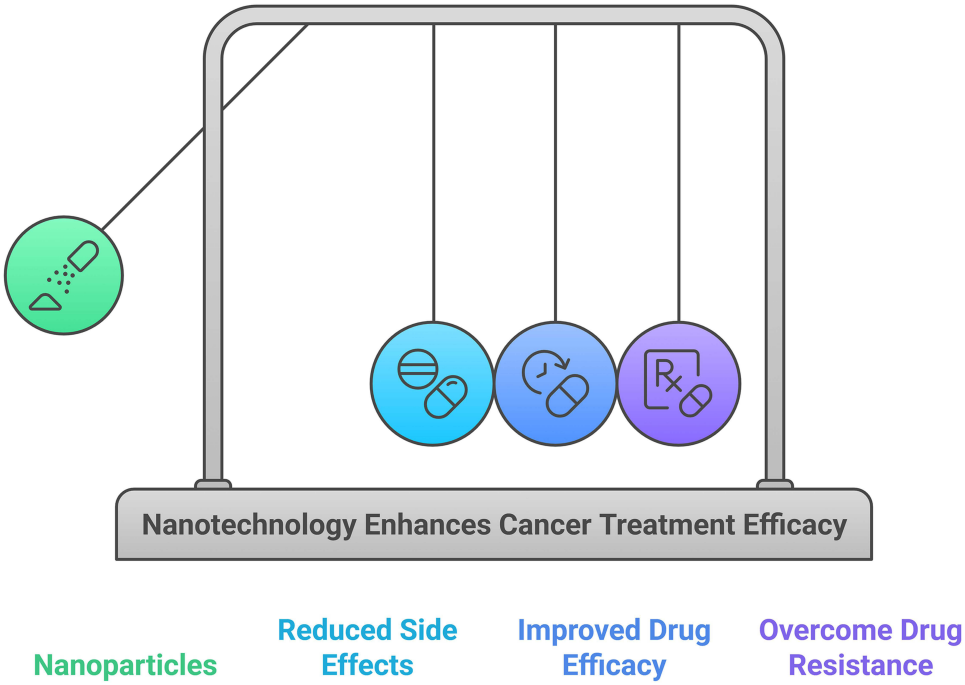
Graphical Abstract



nanocarriers (NCs) are an emerging platform that can be tailored in terms of tumor pathophysiology to enhance therapeutic properties, tumor permeability, and drug retention time. Similarly, using NPs for therapeutic encapsulation makes it possible to reduce the chemotherapy-associated adverse side effects.[10] Such nanosystems can increase the therapeutic index and tumor tissue concentrations, enhancing the efficacy of current regimens. Benefits include overcoming solubility and stability challenges, protecting drugs from degradation, enhancing drug distribution and targeting, facilitating sustained drug release, enabling multiple drug delivery, and reducing drug resistance.[11] Nanoscale drug delivery systems (NDDS) offer several advantages in targeting cancer, like targeted drug delivery, multifunctional targeting, and tumor selectivity. These systems can provide a controlled and sustained drug release condition, perform multiple functions, and target tumor lesions either passively or actively.[9,12] NDDS can extend the drug's half-life and improve its uptake in the tumor, based on the size and surface properties of NPs. Nanotechnology has transformed drug delivery by enabling medications to enter previously inaccessible target areas of the body, such as transversing the blood-brain barrier (BBB) for neurological disorders/cancers.[2] The NPs can release drugs in response to stimuli like light, pH, temperature, electromagnetic waves, magnetism, and ultrasound. Based on the physicochemical properties of drugs, customized nanocarriers can be designed to avoid unwanted clearance by macrophages and the kidneys.[7] On the contrary, new technologies, like theranostic materials, combine therapeutic agents with imaging capabilities to monitor real-time treatment responses.[13] Additionally, the development of personalized nanocarriers tailored to the molecular profiles of individual tumors enhances targeting and therapeutic efficacy, paving the way for more effective and individualized cancer treatment strategies.[14]

Many nano-therapeutic drugs have been commercialized or entered into clinical trials in recent years. For example, in 2010, the first clinical trial delivered small interfering RNA (siRNA) to patients with solid cancers using a targeted NP-based system.[2] Herein, different types of nanocarriers and details on their composition, preparation method, and functionalization, as well as loaded drugs/active agents, have been reviewed, and the validation of each system in specific cancer-related applications has been highlighted.

Understanding Drug Resistance in Cancer Therapy

Drug resistance is a substantial obstacle to effective cancer treatment, accounting for approximately 90% of chemotherapy-associated failures.[15,16] Multi-drug resistance (MDR) is a condition in which cancer cells develop resistance to various anticancer drugs, thereby diminishing the efficacy of the treatment. Higher doses of chemotherapy agents have been used to tackle MDR, but this approach frequently results in increased toxicity and may potentially damage healthy organs and tissues.[17,18] This resistance can be classified into intrinsic resistance (present before treatment) and acquired resistance (developed during therapy) and is mediated by key genetic alterations and associated pathways. Oncogenes like KRAS and BRAF activate the MAPK/ERK signaling pathway, promoting cell survival, while HER2 overexpression activates the PI3K/AKT/mTOR pathway, contributing to resistance against therapies like trastuzumab.[19,20] Tumor suppressor genes such as TP53 and BRCA1/BRCA2 are critical; mutations in TP53 disrupt apoptotic pathways, and alterations in BRCA genes impair DNA repair, leading to increased genomic instability and resistance to agents like cisplatin. Drug metabolism and efflux mechanisms, such as the overexpression of permeability-glycoprotein (P-gp), reduce the effectiveness of chemotherapeutic agents. Epigenetic modifications, including aberrant DNA methylation by DNA methyltransferases (DNMTs), can silence tumor suppressor genes, while histone modifications may impact drug sensitivity.[19,20] Microsatellite instability (MSI) from DNA mismatch repair defects increases mutation rates and affects immunotherapy responses. Gene rearrangements like the BCR-ABL fusion gene activate tyrosine kinase signaling, contributing to resistance in chronic myeloid leukemia (CML). Cancer stem cells (CSCs) exhibit enhanced DNA repair and high drug efflux pump expression, making them resistant to conventional therapies. Alternative pathway activation, such as the MET signaling pathway, allows cancer cells to evade targeted therapies.[19,20] There are a number of potential causes of MDR in cancer cells which revealed in Figure 1,[21] including overexpression of drug efflux systems (Figures 1A), deregulated apoptosis process, and alterations in cell signaling pathways (Figure 1B–D), DNA repair mechanisms (Figures 1E and F), tumor heterogeneity, genetic and epigenetic modifications in cells (Figure 1I–L).[17,21] Generally, the cooperation of these mechanisms leads to drug resistance.[22] One example of MDR is seen in patients with metastatic non-small cell lung cancer (NSCLC) who acquire resistance to epidermal growth factor receptor (EGFR) inhibitors.[23] Insufficient drug delivery to deep tumors and continuous exposure to sub-lethal doses of cytotoxic drugs are factors that promote drug resistance.[17] Also, molecularly-targeted therapies, like tyrosine kinase inhibitors and antibodies, can cause drug resistance. The resistance is imparted by the growth of resistant cancer cell populations, shifts in target expression, and adaptation of immune evasion mechanisms. These therapies may contribute to the selective proliferation of CSCs. CSCs are a small subset of cells within tumors capable of self-renewing, developing new tumors, and resisting traditional cancer treatments. CSCs are crucial in driving cancer progression, heterogeneity development, and relapse. Addressing drug resistance and adequately eradicating CSCs in tumors is crucial to enhancing treatment effectiveness and increasing survival rates.[22]

Mechanisms of Drug Resistance

Drug Efflux Pumps

MDR in tumor cells is primarily caused by the increased expression of drug efflux pumps, specifically adenosine triphosphate (ATP)-binding cassette (ABC) proteins (Figure 1A).[18] These proteins, classified into various subfamilies (ABCA, ABCB, ABCC, ABCD, ABCE, ABCF, and ABCG), are crucial in pumping out chemotherapeutic drugs from the cell, reducing their therapeutic concentration. One of the well-known efflux pumps is P-gp, encoded by the MDR1 gene. P-gp is highly expressed in cancer cells and is associated with low therapeutic efficacy, especially in colorectal cancer (CRC). Its overexpression leads to the expulsion of drugs like paclitaxel (PTX) and doxorubicin (DOX), resulting in drug resistance.[21,24] Advanced DDS, known as nanomedicines, have been developed to overcome MDR. These systems utilize NPs, nanotubes, micelles, liposomes, and metal nanomaterials to bypass P-gp-mediated drug efflux. NPs can achieve drug release under specific conditions such as pH, hypoxia, and reducibility, allowing drug accumulation in tumors through passive targeting effect, ie, enhanced permeability and retention (EPR) effect or active targeting, ie, ligand-receptor binding (Figure 1A). They can also utilize the endosome-lysosome pathway to transport drugs into cells instead of relying on passive diffusion. Certain substances or groups, such as clathrin, can attach to glycoproteins or lipoproteins on the cell membrane, causing the membrane to curve and form early endosomes. These endosomes can then

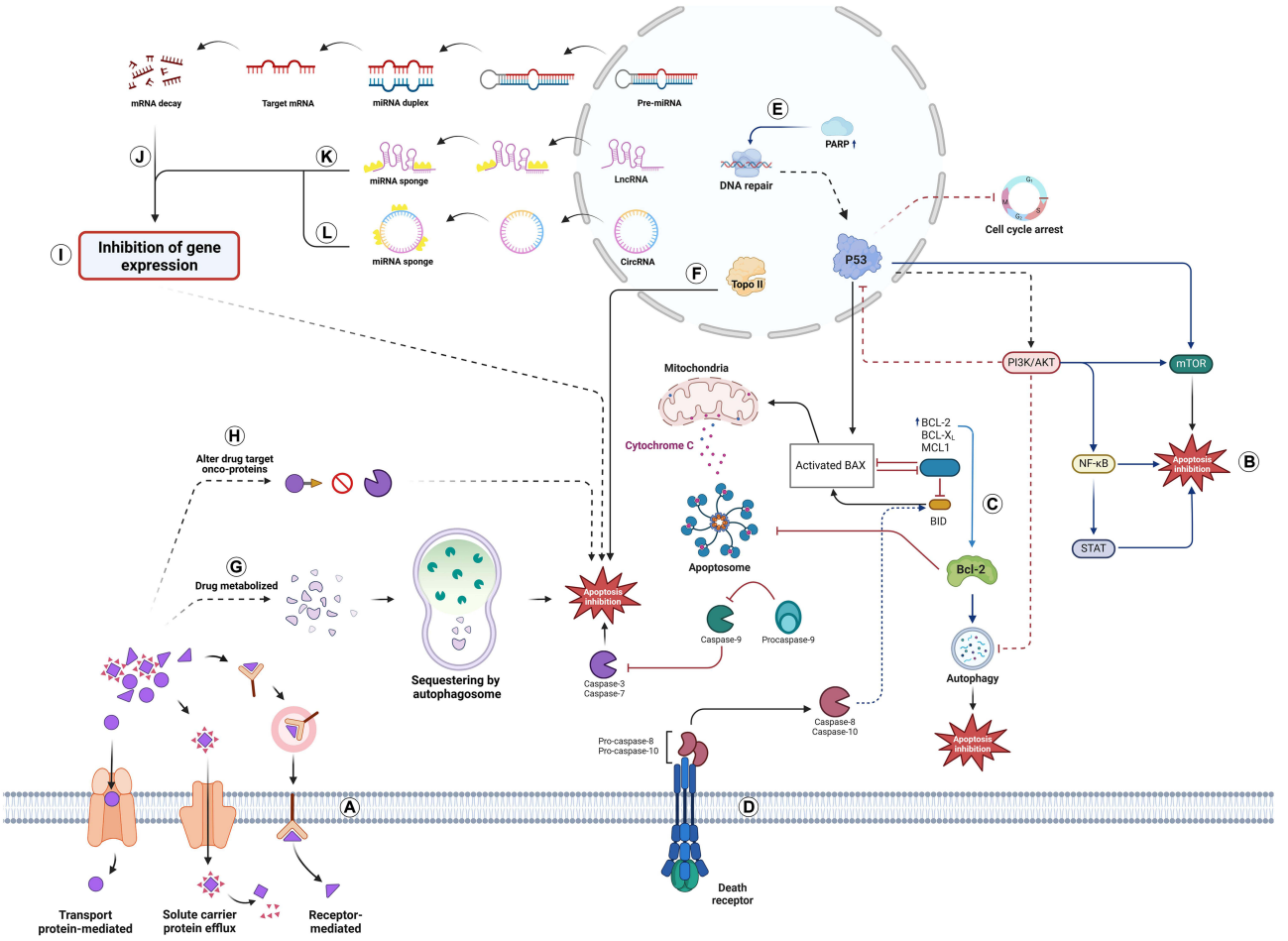


Figure 1 An overview of drug resistance mechanisms in cancer cells. (**A**) Anti-cancer Drug Efflux: Cancer cells depend on various transport mechanisms, including solute carrier (SLC) protein, receptor-mediated, and transport protein-mediated efflux, to expel anticancer drugs, thereby reducing their intracellular concentrations. (**B–D**) Apoptosis blocking pathways: Reveal the crosstalk between intrinsic and extrinsic through the signaling pathways. In IIA these pathways are involved in regulating apoptosis and their activation promoting apoptosis inhibition; In IIB, the loss-of-function of p53 and inhibition of pro-apoptotic signals, such as increased BCL-2 levels, prevents the formation of the apoptosome, a critical complex for initiating apoptosis; In IIC, the death receptor pathway can trigger apoptosis through receptor-mediated mechanisms by activation of caspases while dysfunction promoting survival signals. (**E**) DNA Repair Pathway Activation: Increased levels of poly (ADP-ribose) polymerase (PARP) enhance DNA repair mechanisms, allowing cancer cells to survive DNA damage caused by therapies. (**F**) Decreased Topoisomerase II Activity: Reduced activity of Topoisomerase II contributes to the resistance against drugs that target DNA replication and repair. (**G**) Drug Metabolism: Anticancer drugs are metabolized within the cell, forming metabolites that autophagosomes can sequester. (**H**) Alteration of Drug Targets: Oncogenic proteins may be modified, diminishing the effectiveness of targeted therapies. (**I-L**) Inhibition of Gene Expression: The presence of sponges on microRNA (miRNA) (VA) leads to the degradation of target mRNA; in circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs) resulting in translational repression and leads to inhibiting the expression of pro-apoptotic genes and promoting survival pathways.

encapsulate NPs or other cargo and transport them inside the cell. This mechanism, clathrin-mediated endocytosis (CME), has been extensively utilized in reversing MDR.[18] Solute carrier (SLC) transporters (Figure 1A) also play a crucial role in cancer drug resistance by regulating the cellular uptake of anticancer drugs and essential nutrients. The expression levels of SLC transporters in tumors and host tissues significantly impact drug efficacy, side effects, and interactions. Downregulation of SLC transporters in cancer cells can lead to ineffective therapy.[25] This resistance mechanism has been observed in various malignancies, including multiple myeloma.[26] In multiple myeloma, both ABC and SLC transporters contribute to resistance against novel therapies like proteasome inhibitors and immunomodulatory drugs.[26] To target the problem of drug efflux pumps, novel efflux pump inhibitors can be screened using small-molecule/natural product/repurposed drug libraries, screening for anti-adaptive molecules, designing peptide-based inhibitors, and applying CRISPR Cas to fine-tune their functions. Among the other interesting approaches are prodrug design, photosensitizers, and photodynamic therapy (PDT) to damage drug efflux pumps, as well as artificial intelligence (AI)-based structural modification of potential drug candidates.

Inhibition of Apoptosis Pathways

Most anticancer treatments aim to induce apoptosis, or programmed cell death, in tumor cells.[27] Cell death is primarily regulated by necrosis, apoptosis, and autophagy.[28] Apoptosis occurs through two pathways: the intrinsic pathway is controlled by mitochondria and involves B-cell leukemia/lymphoma 2 (BCL-2) family members, caspase-9, and protein kinase B (or Akt) (Figure 1B and C). The extrinsic pathway is initiated by death receptors on the cell surface (Figure 1D). Both of these pathways converge through caspase-3 and 7 activation, resulting in apoptosis. However, there are additional interactions between the pathways. In various cancers, the overexpression of anti-apoptotic proteins, viz, BCL-2 and Akt, and the increased activity of downstream transcription modulators like NF-κB and STAT are observed, making them promising drug targets. Resistance to chemotherapeutics can be associated with the up-regulation of anti-apoptotic (eg, BCL-2, AKT) and down-regulation of pro-apoptotic genes (eg, Bax, Bcl-xL) in tumor cells. An imbalance between anti-apoptotic (such as BCL-2, Mcl-1, and Bcl-xL) and pro-apoptotic proteins (such as Bax, Puma, Noxa, Bak, Bil, and Bid) has been linked to drug resistance in cancer.[24,28] Overexpression of BCL-2 can reduce tumor cell death and lead to treatment resistance. Studies have shown that excessive BCL-2 expression can contribute to MDR in lymphoma cells, colon cancer, and gastric cancer. This upregulation of BCL-2 can diminish the apoptosis triggered by chemotherapeutic drugs and decrease the cells' susceptibility to these drugs. BCL-2 overexpression has also been shown to increase cellular resistance to drugs like cisplatin (CP), docetaxel (DTX), and methotrexate (MTX). Mutations in apoptotic functions can mediate MDR in tumor cells, making them resistant to many chemotherapeutics that induce apoptosis. These mutations also play a crucial role in carcinogenesis and cancer development. For example, the wild-type P53 gene regulates normal cell growth, triggers programmed cell death, and prevents abnormal cell growth (Figure 1E and F).[16] However, the mutant P53 gene can render cellular DNA damage irreparable, compromising the link between DNA damage and apoptosis induction.[16,28]

Reduced Drug Uptake

Drug Inactivation

The other drug resistance mechanism may be the drug's lack of activation or inactivation due to alterations in enzymatic conditions associated with cancer (Figure 1G).[29] In vivo, drug activation involves complex interactions between proteins and substances, potentially forming complexes or undergoing partial degradation. Many anticancer medications require metabolic activation for clinical efficacy, yet diminished activation may lead to tumor cell resistance, highlighting the importance of careful drug activation.[30] An illustrative instance is the alteration and reduction of phosphorylation occurrences in converting Cytarabine (AraC) to AraC-triphosphate, a substance employed in treating acute myelogenous leukemia (AML).[24] AraC does not affect the cancer cells, but its phosphorylated form is lethal in many cancers. Down-regulation or mutations that induce phosphorylation reduce the AraC activity, resulting in drug resistance. Additional examples of drug activations and inactivation mechanisms include the cytochrome P450 (CYP) system, glutathione S-transferase (GST) superfamily, and UDP-glycosyltransferase (UGT) superfamily.[31] Synthetic lethality, generation of resistant prodrugs, new nanocarriers, and dual inhibitors can be interesting ways to target drug inactivation.

Alteration of Drug Targets

Targeted therapy utilizes medications that effectively damage cancer cells and specifically target crucial elements like genes, proteins, or the environment of cancer-specific tissues, which impedes cancer growth and enhances overall survival rates. However, the cancer cells can become resistant by modifying these pharmacological targets via genetic mutations or shifts in epigenetic gene expression (Figure 1H).[32] An example of resistance caused by modifications to the therapeutic target is the identification and use of estrogen-related receptor inhibitors in breast cancer treatment. Patients with estrogen receptor (ER)-positive breast tumors are often prescribed tamoxifen (TAM), which functions by competing with estrogen for the ligand-binding domain of the ER. However, extended exposure to TAM usually leads to drug resistance. The resistance mechanisms can differ among cases, but two prevalent mechanisms include mutations in the ER gene and reduced expression of the ER.[30]

Role of Non-Coding RNAs

MicroRNAs (miRNAs) are short non-coding RNA (~21-24 nucleotides) molecules that regulate gene expression (Figure 1I).[28,33] They are too small to code for proteins but are involved in controlling the expression of protein-coding genes, including those involved in cancer and drug resistance.[28] Altered expression of miRNAs in cancer cells can lead to the development of MDR by misregulating the expression of genes essential for MDR.[16,33] Research has shown that miRNAs can amplify tumor-promoting genes or genes related to apoptosis, cellular proliferation, and the cell cycle. Depending on its target tissue, the same miRNA can enhance or hinder chemotherapy resistance. For example, in breast cancer, increased expression of miRNA-21 leads to a decrease in the expression of PTEN protein, impacting the effectiveness of DOX in tumor targeting. Conversely, when PTEN is overexpressed, the expression of miRNA-21 is suppressed, reducing the resistance of breast cancer cells to DOX.[24] Recent research has focused on the 3' half of the miRNA's involvement in target selectivity and gene regulation, suggesting that nucleotides outside the seed can influence miRNA function and existence, and can be investigated further. Moreover, recent advances in machine learning (ML) can help decipher drug-miRNA interaction, discovery of miRNA therapies, miRNA-miRNA pairings, generating miRNA disease-association models, miRNA treatment prediction, and determining synergy (Figure 1J). Long non-coding RNAs (lncRNAs) (Figure 1K) regulate drug resistance by influencing ATP-binding transporter expression, DNA damage response, epithelial-mesenchymal transition (EMT), apoptosis, and cancer stem cell formation.[34] They are involved in resistance to multiple cancer drugs, including platinum drugs, TAM, trastuzumab, 5-fluorouracil (5-FU), PTX, and androgen deprivation therapy across the top five prevalent cancers.[35] Along with other non-coding RNAs like microRNAs and circular RNAs, lncRNAs modulate the expression of specific target genes and m6A modification involved in drug resistance mechanisms by regulating RNA stability, localization, and translation.[36] Circular RNAs (circRNAs) primarily function as miRNA sponges, regulating gene expression and signaling pathways in drug resistance (Figure 1L).[37] They also regulate drug efflux, apoptosis, autophagy, DNA damage repair, immune cells, cytokines, metabolism, and tumor microenvironment (TME) interactions.[37] They contribute to chemotherapeutic resistance in non-small cell lung and breast cancer by affecting ATP-binding cassette transporters, inhibiting apoptosis, and promoting autophagy.[37,38]

Influence of Tumor Microenvironment (TME)

Cancer cells can manipulate their surrounding area by releasing signaling networks that benefit their growth and survival. This interaction with the TME allows cancer cells to adapt and overcome stressful conditions, leading to cancer progression, metastasis, and drug resistance.[10] The TME consists of various stromal cells, including tumor-associated macrophages,[27] as well as abnormal physiological and biochemical characteristics such as low pH, hypoxia, and high levels of intracellular glutathione (GSH).[27] Hypoxia, a condition of low oxygen levels, is commonly experienced by tumors due to uncontrolled cell growth and inadequate blood supply.[16] The transcription factor HIF-1α plays a crucial role in hypoxia, as its overexpression has been observed in many human cancers.[16] HIF-1α is rapidly degraded under normal oxygen levels, but under hypoxia, it escapes degradation and forms a functional heterodimer with the HIF-1β subunit. This heterodimer enters the nucleus and activates genes related to vascularization, metastasis, and drug resistance. HIF-1α also contributes to chemotherapy resistance in cancer cells.[33,39] Nanocarrier-based strategies have been explored to target cancer hypoxia and improve the therapy, including the encapsulation and delivery of hypoxia-activated prodrugs (HAPs) to hypoxic cancers (Figure 2).[22] To combat MDR cases, researchers are developing advanced nanocarriers that can bypass efflux pumps like P-gp. These nanoparticles can be engineered to release drugs in response to the acidic environment of tumors, which enhances drug accumulation in resistant cancer cells.[40] For example, nanocarriers that encapsulate siRNA targeting P-gp inhibit its expression, thereby increasing the concentration of chemotherapeutics in resistant cells. Furthermore, the development of dual-action nanocarriers that respond to both pH and temperature changes allows for targeted delivery to resistant tumors.[41] Combination therapy formulations that deliver both chemotherapeutics and agents inhibiting resistance pathways, such as paclitaxel alongside a P-gp inhibitor, represent promising strategies to overcome MDR in cancer treatment.[42]

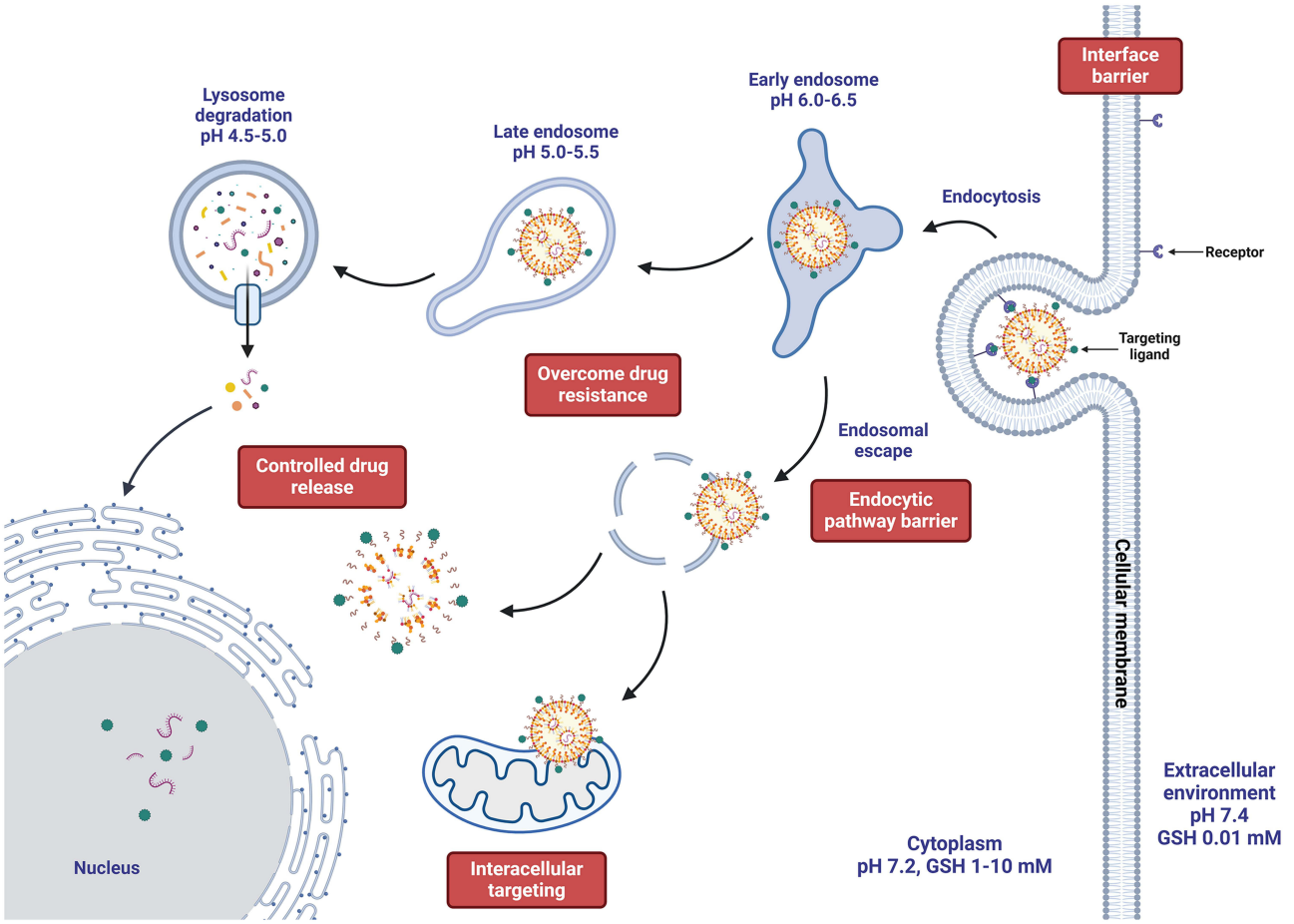


Figure 2 Schematic illustration showing how nanocarriers overcome the cellular barriers for drug delivery. Nanocarriers could deliver drugs into subcellular locations by passing a cascade of barriers, including interface barrier, endocytic pathway barrier, drug resistance, subcellular targeting barrier and controlled drug release.

Targeting Mechanism of Nanocarriers

Engineering drug and gene delivery systems that are able to target affected cells with no influence on healthy cells is a significant challenge in cancer treatment. Understanding the biology of tumors and the interaction of nanocarriers with cancer cells is crucial to tackling therapeutic challenges and developing effective and efficient nanocarrier systems.[43] Targeting strategies to deliver drugs and active agents to the desired organs and tissues include passive, active, inverse, ligand-mediated, physical, dual, double, and combination targeting (Figure 3).[44]

Passive Targeting

Passive targeting is a drug delivery system that targets the drug to the systemic circulation (Figure 3A).[45] Nanocarrier-based cancer therapies primarily consist of first-generation nanomedicines that rely on passive targeting. The first-generation nanocarriers regulate biodistribution and pharmacokinetics by modulating the EPR effect, thereby enhancing nanomedicine accumulation in tumor cells.[5] While the smaller particles have higher penetrability without leaking into normal vessels, the larger particles are more susceptible to being eliminated by the immune system.[2] Solid tumors have inherent abnormalities of tumor vasculature, which can be effectively exploited for targeted delivery of anticancer NP agents. However, large-sized drugs cannot penetrate tight endothelial junctions of normal blood vessels, resulting in a long plasma half-life, which builds up in tumor tissues due to their abnormal vascular nature.[44] EPR effect-based passive targeting is inefficient in controlling cytotoxic drug side effects and can negatively affect drug delivery due to cancer heterogeneity and stroma.[5]

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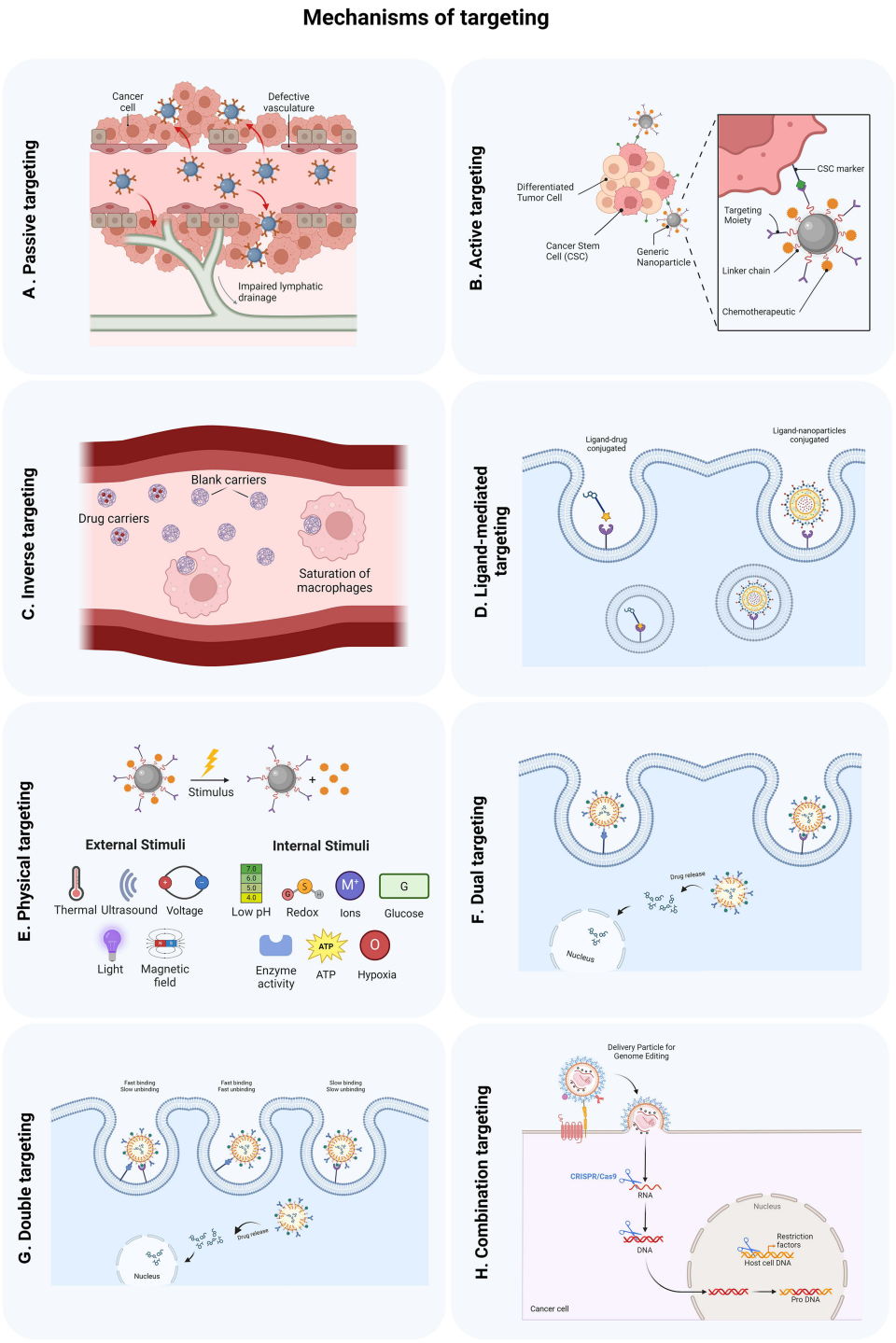

Figure 3 Different strategies of drug targeting. (**A**) Passive, (**B**) Active, (**C**) Inverse, (**D**) Ligand-mediated, (**E**) Physical, **F**) Dual, (**G**) Double, (**H**) Combination.

Active Targeting

This strategy includes drug targeting by identifying a particular set of cells and attaching a drug delivery system to their receptors (Figure 3B).[45] Active targeting methods incorporate ligands, such as antibodies or small organic molecules, which facilitate the uptake by the targeted cells. These ligands can target surface molecules expressed in the diseased cells, proteins, sugars, lipids in the organs, and molecules in the diseased cells' microenvironment or the physicochemical environment.[46] Ligands on the surface of NPs are selected to target the molecules overexpressed on the surface of cancer

cells, allowing them to distinguish between healthy and targeted cells. The interaction between NPs' ligands and cancer cells' receptors triggers receptor-mediated endocytosis, enabling the successful release of therapeutic drugs. This active targeting approach is particularly suitable for delivering macromolecular drugs like proteins and siRNAs.[2] This way, direct tumors or the mildly acidic TME, the TME's vascularization, or the tumor nucleus can be targeted.

Inverse Targeting

Inverse targeting of drugs occurs when the reticuloendothelial system (RES) prevents colloidal carrier absorption, suppressing its regular function, which is achieved by pre-injecting blank carriers or macromolecules such as dextran sulfate, facilitating RES saturation and suppressing defense mechanisms, making it a practical method for targeting drugs to the non-RES body organs (Figure 3C).[44]

Ligand-Mediated Targeting

Ligands are affixed to carrier surfaces, guiding the carrier to designated locations. Colloidal carrier systems may be functionalized with biologically relevant molecular ligands like antibodies, polypeptides, oligosaccharides, viral proteins, and fusogenic residues. These ligands facilitate recognition and specificity, allowing targeted drug delivery (Figure 3D).[47]

Physical Targeting

This approach employs environmental changes like pH, temperature, light intensity, ionic strength, electric field, and specific stimuli like glucose concentration to locate the drug carrier, making it optimal for tumor targeting and cytosolic delivery (Figure 3E).[12]

Dual and Multiple Targeting Approaches

The dual targeting mechanism enhances the therapeutic effect by synchronizing carrier molecules with antiviral drugs, eg, enhancing the therapeutic effect when entrapped in a carrier molecule with antiviral activity (Figure 3F).[45]

The double targeting strategy combines the temporal and spatial methodologies to target specific organs, tissues, cells, or subcellular compartments with a controlled drug release rate to the target site (Figure 3G).[12]

Combination Targeting

These systems, which include carriers, polymers, and molecularly specific homing devices, provide a direct targeting approach (Figure 3H). [48] Recent studies have explored hybrid targeting strategies that combine passive and active targeting mechanisms to enhance drug delivery to tumors. Nanoparticles can be engineered to exploit the enhanced EPR effect, which allows them to accumulate in tumor tissues due to leaky vasculature.[49] Additionally, these nanocarriers can be functionalized with ligands that specifically bind to overexpressed receptors on cancer cells, such as HER2 or folate receptors, enhancing tumor cell uptake.[50] Magnetic nanoparticles that can be guided to tumor sites using external magnetic fields further enhance targeting precision, reducing systemic exposure and improving therapeutic outcomes.[51,52]

Impact of Nanocarrier Physicochemical Properties

Understanding the physicochemical properties of NPs is crucial for improving their concentration and functionality in tumor tissues.[53] While advancements have been made in drug nanocarriers, few have been effectively implemented in clinical studies. The properties of these nanocarriers influence their in vivo biological barriers, which can affect the therapeutic index of the cargo and the desired outcome.[54] Comprehension of the physicochemical peculiarities of nanocarriers is essential since their size, shape, surface charges, and chemistry affect drug distribution, behavior, and delivery efficiency.[54]

Shape

The shape of nanocarriers is an important property affecting their behavior in vivo. Different shapes, such as rods or spheres, can impact processes like uptake by macrophages, circulation in the blood, distribution in tissues, and targeting of diseases.[54] Factors like the curvature structure of NPs and the time needed for cell membrane wrapping can influence

the interactions between nanocarriers and biological systems. For example, rod-shaped NPs have a larger contact area with cell membrane receptors but longer internalization than spherical NPs.[53] Gold nanorods have lower uptake efficiency than spherical particles, which decreases as the aspect ratio increases.[55] Anisotropic nanocarriers with a non-uniform shape have distinct interactions with cells and drugs. Their increased surface area allows for better drug encapsulation and delivery through localized degradation. Additionally, their larger surface area facilitates binding to specific cells and enhances targeting.[56]

Size

The size of nanocarriers is a crucial physicochemical characteristic affecting their in vivo behavior since it directly influences the available surface area for interaction with biological environments. Plasma proteins attach to nanocarriers, creating a protein corona, which gives them a unique "biological identity" and determines their interactions with the phagocytes.[54] While nanocarriers of less than 5 nm in diameter can be rapidly cleared from the blood, those of more than 15 μm can be accumulated in the liver, spleen, and bone marrow. The optimal size for DDS is currently considered 100–200 nm, as this size allows the EPR effect in tumors and avoids filtration in the spleen.[57]

Surface Chemistry

Surface chemistry design plays a critical role in the development of nanomaterials for biomedical applications. Research studies have shown that the surface chemistry of polymer-based nanomaterials significantly affects their interactions with cells.[46] Surface modification of NPs ensures their stability in physiological environments. However, the reactive nature of NP's surface can also influence biological responses.[58] Surface functionalization of NPs prevents their aggregation and minimizes the non-specific cellular absorption. Additionally, surface chemical modification can reduce the potential hazards of NPs and establish a safe-by-design approach for their future use. Overall, surface chemistry design is essential for optimizing the performance and safety of nanomaterials in biomedical applications.[53]

Surface Charge

The surface charge of NPs is critical to their interaction with biological systems. Their surface charge influences cellular uptake, while positively charged nanocarriers show better internalization and higher efficiency than negatively charged ones.[46] However, the positive surface charge also rapidly removes NDDSs from the bloodstream. The interaction between negatively charged albumin and positively charged NPs is the main factor in removing cationic nanocarriers.[59] Surface charge also affects the fate of nanocarriers in vivo by influencing the biodistribution, opsonization process, and plasma protein adsorption. High surface charge densities lead to an acceleration of blood clearance and capture by the RES, while neutral charges promote prolonged blood circulation and reduced clearance by the RES.[54]

Types of Nanocarriers in Cancer Therapy

Nanocarriers are colloidal particles smaller than 500 nm that are used to encapsulate drugs and biological materials. They can be made from various materials, including (i) organic NPs, such as solid lipid NPs, polymeric micelles (PMs), liposomes, nanoemulsions (NEs), polymeric NPs, and exosomes, (ii) inorganic NPs, such as carbon-based nanomaterials, metals and metal oxides, quantum dots (QDs), and (iii) hybrids (Figure 4). Stimuli-responsive nanocarriers are the third generation of controlled-release DDS, allowing precise drug release within target cancer cells. Their benefits include improving drug pharmacokinetics and biodistribution, enhancing solubility and permeability, minimizing therapeutic doses, and reducing toxicities. At the same time, modifying the properties, such as composition, size, shape, and surface properties of nanocarriers, can protect drugs from premature degradation to overcome MDR in cancer cells. Cancer cell-targeted drug delivery strategies often involve nanocarriers with cancer cell-specific ligands on their surface and mechanisms that cause the release of drugs within the cytoplasm of cancer cells.[60] The development of third-generation nanocarriers, including stimuli-responsive and hybrid systems, marks a significant advancement in cancer therapy. These carriers can be designed to release their drug payloads in response to specific triggers such as temperature or light, allowing for controlled drug release at the tumor site.[61,62] For instance, light-activated nanocarriers can release DOX upon exposure to specific wavelengths of light, while biodegradable polymeric nanoparticles made from materials like poly(lactic-co-glycolic acid) (PLGA) degrade into non-toxic byproducts, enhancing safety and reducing long-term

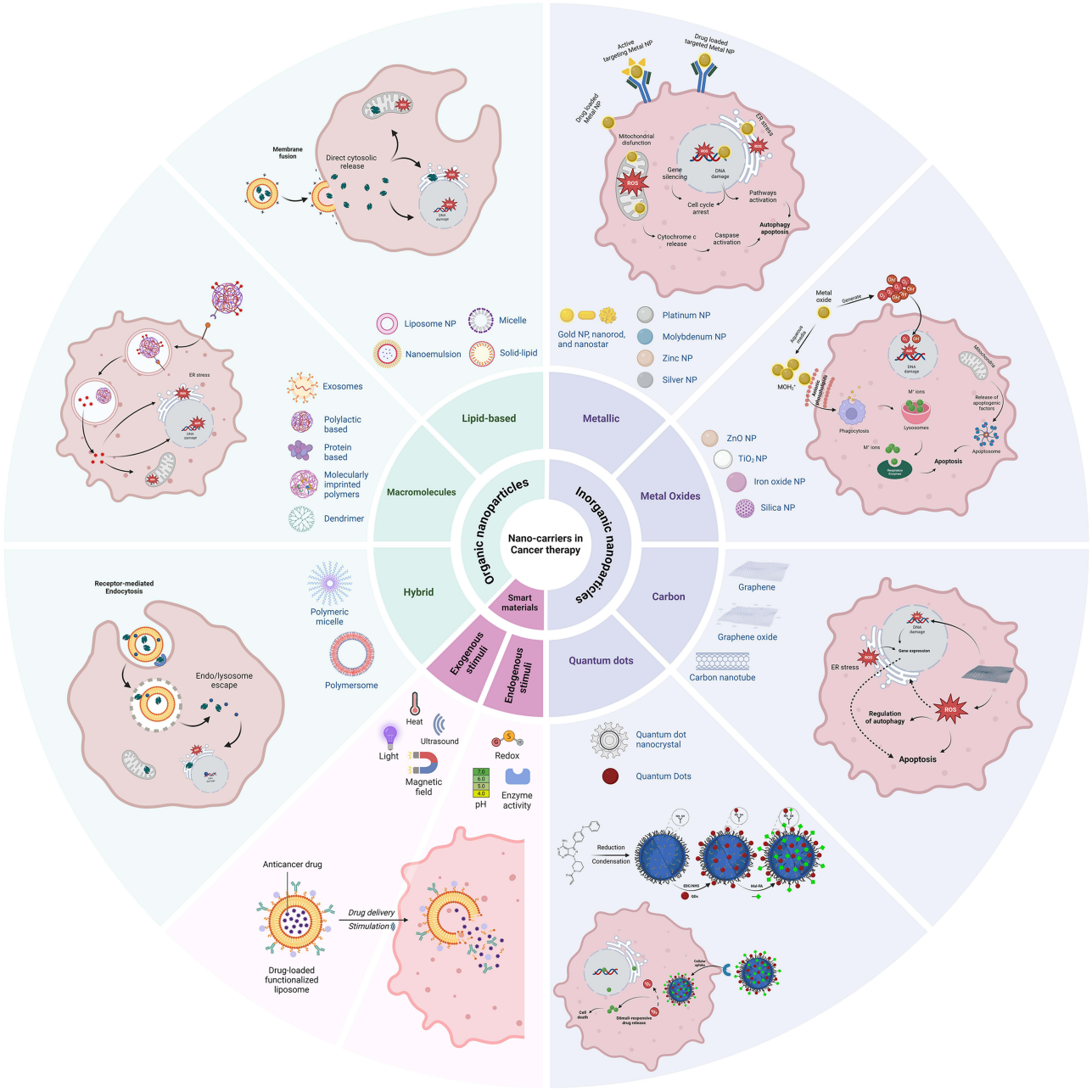

Figure 4 Classification of nanocarriers for cancer therapy.

toxicity.[63] Additionally, temperature-sensitive nanocarriers that release drugs in response to hyperthermia enable localized treatment of tumors, providing a targeted approach to cancer therapy.

Organic Nanocarriers

Lipid-Based Nanocarriers (LBNCs)

LBNCs, a class of nanomedicines with FDA approval, offer benefits like easy formulation, self-assembly, biocompatibility, high bioavailability, large payload capacity, and adjustable physicochemical features. They are classified as liposomes, nano-emulsions, and solid lipids.[64]

Innovations in lipid-based nanocarriers, particularly polyethylene glycol (PEG)ylated liposomes, have improved their circulation time and stability in the bloodstream, enhancing their effectiveness in cancer treatment.[65] Enhanced

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formulations of liposomes, such as Doxil, encapsulate doxorubicin for breast cancer treatment, reducing immunogenicity and improving pharmacokinetics. New developments also involve combination therapy liposomes that co-encapsulate multiple drugs, allowing for synergistic effects against cancer cells.[66] Furthermore, lipid nanoparticles specifically designed for the delivery of messenger RNA (mRNA) vaccines or therapies have shown promise in improving stability and cellular uptake, representing a significant advancement in the field of cancer immunotherapy.[67]

Liposomes

Liposomes, spherical structures made up of phospholipids, are widely used in drug delivery, particularly in cancer treatment. They have several advantages, including compatibility with both hydrophilic and hydrophobic drugs, low toxicity, extended-release potential, and the ability to carry large drug payloads and protect them from the external environment. Because they are biocompatible, biodegradable, and non-immunogenic, liposomes are suitable choices for DDS. However, liposome has limitations, including possible carrier toxicity and challenges in large-scale production and stability.[68–70] One of the most successful applications of liposomes is the delivery of chemotherapeutic drugs/agents for cancer treatment. There are several approved and commercially available liposomal formulations for cancer therapy, such as Vyxeos®, Onivyde®, Marqibo®, DepoCyt®, and Doxil®. In the year 2024, the FDA approved the use of liposomal irinotecan as a first-line therapy for pancreatic adenocarcinoma. These liposomal formulations have shown promising results in improving drug delivery and reducing toxicity.[69] Akbari et al developed nanoliposomes containing hydrophobic hydroxyurea (HU) for breast cancer cell therapy. The HU-loaded nanoliposomes were 174 nm in size, not significantly larger than blank ones, and showed a rapid release over 5 hours, followed by a sustained release for up to 36 hours. This release pattern was attributed to adsorbed HU on the nanoliposome surface, liposome erosion, and HU diffusion mechanisms. The nanoliposomes also demonstrated high cellular internalization and uptake in breast cancer cells, indicating their affinity for the cells, which led to an increased accumulation of HU.[71] To improve the properties of liposomes, researchers have attached PEG to the liposomes and developed PEGylated liposomes,[72] which can prolong the blood circulation and protect the drug from clearance by the mononuclear phagocyte system (MPS).[73] PEGylated liposomes modified with PEG_{2000} have enhanced blood retention.[74] Some ionizable cationic liposomes have a surface charge of neutrality under physiological conditions after being loaded with nucleic acids.[75,76] Altering the composition of liposome head groups, lipid tails, and cholesterol quantity can also affect cellular uptake and tumor penetration in specific cancer types like glioblastoma and triple-negative breast cancer (TNBC).[77] Liposomes have emerged as a promising tool in gastric cancer therapy, mainly combined with SATB1 siRNA, CD44 antibodies, and DNA complexes. These formulations facilitate enhanced drug accumulation in tumor-bearing mice, demonstrating superior targeting precision and effective silencing of SATB1 gene expression in CD44+ gastric CSCs. This approach significantly improves the therapeutic efficacy for this challenging cancer type.[78] Additionally, Myocet®, a non-PEG-DOX liposome, has been utilized in temozolomide-based chemotherapy for high-grade glioma, establishing the maximum tolerable dose for patients aged 28 to 65 and diagnosed with gliomas who received nanoliposomal irinotecan.[79] Furthermore, the combination of PEG-DOX liposomes with lapatinib is the most effective treatment strategy for individuals with HER2-positive breast cancer. In xenograft models, liposomal formulations loaded with DOX and Apache have been reported to elevate DOX levels in tumor tissues, enhancing therapeutic outcomes.[80] Liposome nanoparticles, due to their unique structure, have been used in cancer therapy through gene therapy.[81] They were applied in gene therapy through encapsulation of siRNA molecules and regulating the responsible genes in the multiplication of cancerous cells through gene modulation and silencing.[82] In addition, liposomal nanoparticles helped destroy and kill cancer cells by delivering plasmid DNA- encoding tumor suppressors to tumor sites. Liposomes have also been used to deliver various diagnostic agents, such as[64] Cu,[14,83] Cisotopes,[84] QDs,[85] gadolinium (Gd)-based contrast agents,[86] etc. Researchers hope that liposomes will soon be used as a simultaneous carrier of therapeutic drugs and diagnostic agents for cancer patients in clinical trials. Clinical trials have shown that liposomal formulations, especially liposomal doxorubicin, effectively treat various cancers like breast, ovarian, and lung cancer. Research highlights its cardiac safety and effectiveness as a standalone treatment and in combination with other therapies.[87] Recent advancements include thermosensitive liposomes that release drugs in response to temperature changes, enhancing targeting and reducing side effects.[88] In pediatric oncology, the use of liposomes is limited, but optimizing their design could improve drug delivery for children with

cancer.[89] Innovative approaches, such as dual pH-responsive liposomes, are being explored to release drugs specifically in tumor environments, while combining liposomes with immunotherapy shows potential for enhanced anti-tumor effects.[90] The use of liposomal DNA delivery and DNA barcoding can be an efficient method to predict treatment responses.

Solid Lipid Nanoparticles

Solid lipid NPs are physiological fluids (room and body temperature) used to administer colloidal drugs, ranging from 50 to 1000 nm.[91] These particles are contained within a drug-encapsulating matrix made of glycerides/fatty acids complex combinations.[92] Nanotechnology can enhance patient prognoses. A steroid prepared by cold dilution techniques for chitosan-coated lipid NPs and filled with curcumin (CUR) could inhibit the growth of PANC-1 cells.[93] PTX and 5-FU-charged lipid nanocarriers (such as Intaxel®) were used in managing male patients with LivC, shielding the medication from enzymatic deterioration by its plasma buildup and performance.[94] Sorafenib (SOR) drug and superparamagnetic iron oxide NPs have also been co-loaded in SLNs for the dual treatment of HepG2 cells.[95]

Nanoemulsions

NEs are colloidal mixtures of two non-miscible liquids that exhibit thermodynamic instability. They are used as carriers in cancer treatment to deliver drugs to the targeted site. The drug is enclosed in the core of the NEs, which enhances its bioavailability and reduces its undesired action on other cells or tissues. NEs have droplets with diameters ranging from 10 to 200 nm and a protective coating of emulsifier molecules,[96] which have several advantages in drug delivery. They have a higher drug solubilization capacity, better thermodynamic stability, long shelf life, rapid onset of action, and reduced inter-subject variability.[97] In addition, NEs are non-toxic and non-irritant and permit easy application to the skin and mucous membranes.[98] They can be formulated as foams, creams, liquids, and sprays, and if their formulation contains biocompatible surfactants, they can also be orally administered.[99] NEs are particularly effective in delivering drugs through the skin, and due to their small size, they can penetrate the rough skin surface and enhance the penetration of active ingredients.[98] Several NE delivery systems have been marketed in the past decade for various applications, including ophthalmic treatments for dry eye syndrome and oral immunosuppressive agents.[100] In a study by Miranda et al, a NEs containing a novel fucoside derivative of Lapachol was prepared and characterized for intravenous treatment. The NEs with a size of around 190 nm and a zeta potential close to −20 mV showed excellent drug encapsulation efficiency (nearly 100%). The NEs also demonstrated sustained drug release, with approximately 50% of the drug remaining after 24 hours.[101] The NE oil-in-water formulation, a toxoid drug associated with omega-3 fatty acids, has demonstrated a 12-fold reduction in the toxoid IC50 of PPT2 cells, resulting in a greater reduction in tumor volume in tumor-bearing mice than Abraxane™.[102] Catechin-extract NE has also shown anticancer properties in PC-3 cells.[103] DTX-NE and NE lipophilic diffuse methane show enhanced antitumor activity in A-549 cells. Nebulized DTX NE (MRC-5 cells) has succeeded more than normal cells, creating a standard framework for co-encapsulating gemcitabine (GC) and PTX with a ligand targeting the glucose receptor and revealing the potent synergism.[104] Clinical studies such as Phase III of PTX intratemporal liposome injection have also shown successful results for lung cancer.[105]

Nanoscale lipid-based theranostic systems, particularly lipid-based nanoparticles (LNPs), are prospective carriers for cancer theranostic agents to cure different types of tumors. LNPs can be tailored with different targeting moieties and possess the potential to bypass different physiological barriers and improve the pharmacokinetics. Zhang et al[106] developed a fluorinated nanoemulsion that significantly improved fluorescence imaging signals and revealed effective diagnosis of specific tumors, facilitating photodynamic therapy. Similarly, Hou et al developed a porphyrin shell-nanoemulsion that stabilized the oil core, resulting in a monodisperse nanostructure for imaging and phototherapy.[107] Liang et al developed a theranostic nano platform using smaller (<20 nm) iron oxide loaded with porphyrin-grafted lipid nanoparticles (Fe3O4@PGLNPs), which demonstrated significant photodynamic effects against HT-29 cancer cells in vitro.[108] The negligible toxicity, multifunctional capabilities, and flexibility in functionalization of LNPs position them as a vital tool in cancer theranostics, enabling effective treatment strategies across various tumor types.[109]

Polymer-Based Nanocarriers

Polymeric NPs have gained significant attention in biomaterials and drug delivery due to their unique properties and versatility. These NPs can be synthesized using synthetic and natural polymers, allowing customization and optimization for various biomedical applications.[5,110,111] One of the key advantages of using polymeric NPs as drug carriers is their ability to deliver therapeutic agents directly to the target site, such as inflammation regions or the central nervous system, which is particularly important when dealing with potentially dangerous drugs that need to cross the BBB.[110] Polymeric NPs can have a core-shell structure, with a hydrophilic shell and a hydrophobic core, effectively protecting the drug from degradation.[112,113] They offer a controlled-release potential, allowing for prolonged drug delivery, and can also be manipulated to have different release kinetics, ensuring the drug is released at the desired rate and duration. This is beneficial, especially in the case of chemotherapeutic agents, where site-specific targeting and side effect reduction are crucial. Their distinct features, including drug solubility, stability, and selective accumulation, render them adaptable platforms for delivering therapeutic agents. In addition to drug delivery, polymeric NPs can be used in biomedical applications such as biosensors and catalysis. They can be designed to have different chemical compositions, charges, and physical structures, allowing for customization based on specific requirements.[46] One commonly used polymeric NP is PLGA, known for its biocompatibility, biodegradability, and EPR effect.[114] PLGA NPs have been extensively studied and utilized as drug carriers.[115] For example, Zumaya et al developed a multifunctional PLGA-based nanocarrier system for co-delivering colchicine and purpurin 18 to human cancer cells. They compared the release of colchicine from PEGylated and non-PEGylated PLGA NPs, and the latter nanocarriers exhibited a slower and more sustained release profile.[116] Wu-Cheng et al investigated the use of a nitric oxide (NO) conjugate of albumindinitrosyl iron unit, $[(NO)_2Fe(m\text{-}SCH_2CH_2OH)_2Fe(NO)_2]$ (DNIC-1), for oral delivery to activate hippocampal neurogenesis in chronic neuropathy, demonstrating effective mucosal absorption and sustained NO release without toxic byproducts. On the flip side, DNIU [Fe(NO)2]'s binding affinity to the cysteine residue (thiol group) in serum albumin oxidizes DNIC, which leads to the release of NO without toxic peroxynitrite formation.[117] Yafang Qin et al, in 2022, developed luteinizing hormone-releasing hormone (LHRH) peptide-conjugated tumor targeting ruthenium (II) complex (Ru1-LHRH) that selectively targets the mitochondria, induces apoptosis by inducing reactive oxygen species (ROS) and activating the Caspase3/7 pathway, while imaging property reveals theranostic capabilities.[118] Costagliola di Polidoro et al developed a hyaluronic acid conjugated Angiopep-2 (Thera-ANGcHANPs) for glioma targeting, which enhances imaging and selectively delivers therapeutic agents across the BBB, exhibits significant cytotoxic effects.[119] Yan et al introduced a novel synthetic nanocomplex (NC) to overcome MDR cancer, contained synthetic redox-responsive polyethyleneimine (PEI) polymer (disulfide linked PSP), tetrahedral DNAs (TDNs) loaded with DOX drug (PSP/TDNs@DOX) that enhances drug delivery by creating pores-due to the difference in charge- in the cell membrane and facilitate the internalization of DOX while bypassing endocytosis pathways. PSP/TDNs@DOX NC revealed higher therapeutic efficacy in xenograft drug-resistant tumor mouse models, including human breast cancer (MCF-7/R) and ovarian cancer (SKOV3/R), due to its respond to GSH and DNase I to cleave and release DOX.[120] Cai et al developed a theranostic system based on a small gadolinium chelate with PTX, linked via a cathepsin B-responsive linker, and covalently attaching a fluorescent probe, pheophorbide, to a branched glycopolymer. Their study demonstrated that this multifunctional system, derived from the glycopolymer prodrug in 4T1 xenograft mice, exhibited improved pharmacokinetics, enhanced tumor accumulation, angiogenesis inhibition, excellent biocompatibility, and significantly reduced gadolinium ion retention post-injection. The system also showed prolonged circulation time, a tumor inhibition rate exceeding 90%, and brighter MRI contrast intensity.[121] The Incorporation of targeting ligands, such as antibodies, aptamers, and peptides, enhanced the specificity of these systems. For example, Zhong Yuan Chen et al reported aptamer-dendrimer-functionalized magnetic nano-octahedrons that consist of PAMAM dendrimer, zinc metal doped with superparamagnetic iron oxide, hydrophobic anti-cancer drug DOX, and HSP70/HSP90 siRNAs surface modified by PEG (ZIPPApt: DOX/siHSPs), which combines hyperthermia and as a chemotherapy theranostic system effectively enhanced apoptosis in 4T1 cancer cells.[122] Additionally, Hosseini et al recently developed a theranostic dendrimer system to target CRC by attaching the cetuximab monoclonal antibody to PAMAM G4 and labeling it with Lu-177 via DTPA-CHX chelator on the mouse tumor and SW480 cancer cell line by expressing EGFR. Single-photon emission computed tomography (SPECT) images showed that the system caused apoptosis those cells that expressing epidermal growth factor.[123]

Micelles

Polymeric micelles (PMs) are nanosized molecules with a core-shell structure formed by the self-association of amphiphilic block copolymers in an aqueous solvent.[110] They have gained attention as potential nanocarriers for the controlled delivery of hydrophobic anticancer drugs, which can enhance solubility, extend blood circulation time, improve cellular uptake, and passively target tumor cells through EPR.[115] The advantages of PMs in drug delivery include biocompatibility, low toxicity, core-shell arrangement, micellar association, morphology, size, and stability.[110] Their size (10–100 nm) is critical for the passive targeting of solid tumors, especially poorly vascularized ones. The outer surface of micelles is composed of components that do not react to tissue or blood, allowing them to remain in the blood for a long time without being recognized by phagocytic cells or specific proteins while protecting drug inactivation through the biological environment effect. This longevity is a significant feature of micelles as drug carriers.[124] The core-shell structure of PMs consists of amphiphilic polymers, with the hydrophobic part carrying the hydrophobic drugs and the hydrophilic corona imparting hydrophilicity.[125] Parameters such as cellular internalization, circulation, renal clearance, and the strength of the interface between the hydrophobic core and external aqueous environment are affected by the stability of micelles. The critical micelle temperature and the critical micelle concentration (CMC) determine the spontaneous assembly of micelles and play a key role in micelle formation. While the CMC micelle is formed at lower concentrations, the nanostructure can be dissolved, leading to a premature drug release.[2] Lamey et al found that co-loading dasatinib (DAS) and celecoxib (CXB) into sodium caseinate micelles improved in vivo anti-breast cancer efficacy with reduced drug toxicity. The micelles showed sustained release of both drugs, with a faster CXB release than DAS due to their hydrophobic nature. The drugs' encapsulation efficiency and compatibility with the micellar core influenced the release rate. The dual drug-loaded micelles showed minimal hemolytic rate, indicating low toxicity and also superior tumor growth inhibition in tumor-bearing mice, attributed to better cellular internalization by tumor cells.[126] Another example is the development of a polymeric amphiphilic ionophilic micelle by Lu et al. This micelle had an ultralow CMC and exhibited excellent stability under serum dilution conditions. It enhanced the accumulation of DOX at the tumor site, eradicating melanoma tumors in mice and effectively reversing tumor growth.[127] Genexol-PM is a micellar formulation loaded with PTX that is approved for cancer therapy. It is used for the treatment of NSCLC, metastatic breast cancer, and ovarian cancer.[128] Having developed various novel amphiphilic block copolymers, micelle-based nanosystems have emerged as potential nano-drug delivery vehicles for insoluble drugs.[129] Yun Zhu et al developed PMs containing Chlorin e6 (Ce6) using chitosan and hydrophobic polymethylacrylamide derivatives in another study, which were loaded with chemotherapy agent (DOX) and created Ce6-CSPD/DOX as a theranostic system. The system, which induces apoptosis in cancer cells while restoring fluorescence and photoactive properties.[130] Inoue et al further revealed that combining TGF-β and chloroquine with nano-eruptions in a murine transplant model of GFP-labeled pancreatic tumor cells enhances the drug delivery efficiency and improves the diffusion of PMs through the tumor stroma by increasing tumor vessel diameter (chloroquine) and dynamic valve formation (TGF-b).[131] Additionally, a study involving PEG-PLL conjugated PMs revealed significant accumulation at tumor sites and improved T1 imaging. The distinctive characteristics of polymeric micelles, including high loading capacity and structural flexibility, spot them as promising candidates for theranostic applications, with numerous nanomedicines currently in clinical trials targeting various cancers, particularly for delivering concisely soluble chemotherapeutic agents.[132]

Dendrimers

Dendrimers are a class of polymers extensively studied for their potential applications in nanomedicine,[114] particularly in drug delivery.[133] These artificial polymers have unique structural characteristics, such as high branching and well-defined, monodisperse structures.[134] They can be synthesized at desired sizes and molecular weights, allowing precise control over their properties. One of the critical advantages of dendrimers is their ability to act as carriers for drugs. Due to their unique physicochemical properties and biodegradable backbones, dendrimers can effectively encapsulate drugs and deliver them to specific tissues or cells.[135] The size of dendrimers, typically 2–10 nm in diameter,[136] allows for efficient targeting of cancer cells or injured tissues. Additionally, dendrimers can be functionalized with multiple functional groups on their outer surface, further enhancing their ability to deliver drugs to specific targets.[110] The structure of dendrimers also plays a crucial role in their drug delivery capabilities. The highly branched nature of

dendrimers allows for incorporating multiple functional groups, which can be used to load drugs into the dendrimer core or conjugate targeting ligands onto the surface.[134] This versatility in structure and functionalization enables dendrimers to effectively encapsulate drugs and enhance their solubility, stability, and release profile.[7] For instance, Rai et al encapsulated chrysin in fucose-conjugated poly(amidoamine) (PAMAM) dendrimers and studied its anticancer activity against human lung cancer cells. The dissolution studies showed that the dendrimer formulation significantly improved the solubility of chrysin compared to the free drug. In both acidic and neutral media, the dendrimer formulation exhibited faster dissolution rates and higher drug release percentages than the free drug suspension, which can be crucial for their therapeutic efficacy.[137] Furthermore, dendrimers have shown promise in overcoming the limitations of oral drug administration. The ability of dendrimers to penetrate intestinal membranes allows for improved drug absorption and bioavailability, which is particularly important as the permeability barriers in the gastrointestinal tract often limit the effectiveness of oral drug delivery. By controlling the properties such as size, structure, and solubility, researchers can optimize the dendrimers' ability to overcome these barriers and enhance drug delivery.[2] Due to unique properties, such as well-defined and monodisperse structures, dendrimers are also attractive choices for other biomedical applications, including gene delivery, imaging, and tissue engineering.[138] By modifying the surface functional groups of dendrimers (eg, conjugating targeting ligands onto the surface endings) and loading drugs into their core cavities through hydrogen bonds, chemical linkages or hydrophobic interactions, researchers can tailor their properties to suit specific applications and enhance their performance.[134]

Polymersomes

Polymersomes are nano-sized hollow spherical structures that self-assemble from synthetic polymer/polypeptide amphiphiles, widely used in drug delivery applications. There are two main methods to obtain polymersomes, ie, solvent conversion and organic solvent-free.[139] In the solvent conversion method, a block copolymer is dissolved in an organic solvent. Then, an aqueous phase is introduced, allowing self-assembly to occur. Finally, the organic solvent is removed by dialysis, resulting in the formation of polymersomes. In the organic solvent-free method, the organic solvent is removed by rotary evaporation, and then the system is hydrated to form polymersomes.[140] Polymersomes have a similar morphology and structure to liposomes but are more stable due to their mechanical properties and tunable functions. They consist of a hydrophilic core and a hydrophobic bilayer, allowing the loading of cargoes with different characteristics.[141] One of the critical advantages of polymersomes as delivery systems is their ability to be functionalized for accurate and targeted release at the tumor site.[142] This can be achieved by adding targeted ligands such as antibodies, proteins, and carbohydrates, improving their biological distribution. Optimizing the chemical structure of the block copolymer in response to the tumor's internal and external conditions, such as pH, oxidative stress, hypoxia, and enzymes, is also a practical approach to vesicle delivery.[143,144] Designing polymersomes that are able to respond to these conditions as exogenous-responsive DDS allows for a controlled drug release with reduced side effects, as well as an improved therapeutic efficacy.[143] Zhu et al evolved miRNA-190-Cy7 and Dox co-encapsulated nanoparticles, m-PPDCNPs, revealed no bio-toxicity, high loading efficiency, and precise tumor targeting. The use of membrane-coated PLGA-b-PEG DC-chol nanoparticles (m-PPDCNPs) successfully co-loaded DOX and miR-190, with DOX's encapsulation efficiency reaching 46% and miR-190-Cy7's 88%. Utilizing homologous targeting properties, m-PPDCNPs facilitated effective uptake in CRC cells and enhanced tumor tissue accumulation. The release of miR-190 inhibited VEGF production, thereby reducing tumor angiogenesis. While, miR-190 increased the sensitivity of HCT116 colon cancer cell to DOX, promotes apoptosis and enables combination therapy. Incorporating biomedical imaging, m-PPDCNPs have significant advantages in drug-delivery monitoring, tumor imaging, and vascular therapy. With abilities in drug delivery and monitoring and tumor imaging, m-PPDCNPs represent significant potential for CRC treatment and broader therapeutic applications.[145]

Protein Nanoparticles

Protein-based NPs can transport many molecules, including genetic materials, anticancer medicines, polypeptide hormones, growth factors, DNA, RNA, and more.[146] Protein NPs offer unique advantages compared to other NP-based therapeutics, such as biocompatibility, easy surface modifiability, biodegradability, size controllability, and high

loading capacity.[147–149] They exhibit notable stability and long half-life, overcoming enzymatic degradation and renal clearance, allowing enhanced drug retention and accumulation in tumor tissues. Protein NPs can bind drugs through covalent conjugation and electrostatic /hydrophobic interactions, making them versatile carriers for therapeutic compounds.[150] Various techniques can be used to prepare protein NPs, including emulsion/solvent extraction, complex coacervation, electrospray, and self-assembly.[147] Many proteins can serve as the building blocks for protein-based NPs, such as albumin, collagen, ferritin, gelatin, casein, legumin, gliadin, elastin, whey proteins, silk proteins, soy proteins, and lectins.[151,152] Albumin, in particular, has gained significant attention as a multifunctional nanocarrier for drug delivery[153] because it encompasses both hydrophobic and hydrophilic domains and an abundance of charged amino acids.[154] It is non-toxic, non-immunogenic, cost-effective, and can be produced in a wide size range (20–300 nm).[155] Albumin-bound (nab™)-PTX (nab-PTX; Abraxane®) is an example of an albumin-based NP used for the treatment of various cancers such as NSCLC, metastatic breast, ovarian, and pancreatic cancer.[155] Chen et al generated intelligent multicomponent albumin-coated MnO_2 NPs using a one-step bio-mineralization technique that exhibits pH and H_2O_2 responsiveness, allowing for photodynamic and chemotherapeutic approaches.[156] Environmentally friendly methods have also been employed for the production of albumin NPs, which can encapsulate several drugs and break the BBB without cross-linking agents.[157] Yu et al developed gemcitabine andpheophorbide-a (P@) loaded human serum albumin (HSA) (P@-Gem-HSA) for treating lymphatic pancreatic ductal adenocarcinoma (PDAC) metastases, using human serum albumin (HAS) as a natural transporter (for superparamagnetic iron oxide, organic/inorganic oxides, IR780, IR825, and Ce6)[158] for effective theranostics.[159]

Inorganic Nanocarriers

Metal-Based Nanocarriers

Due to their unique potential and physicochemical properties, metal NPs have attracted researchers' attention, specifically in drug delivery and cancer diagnosis and treatment.[160] These NPs can be synthesized with a controllable size and shape, a stealth ligand-coated surface able to evade the body's immune system and circulate longer in the blood.[161] Metal NPs, such as Ag, Au, Pd, Ti, Zn, and Cu NPs, exhibit improved optical properties and can be functionalized to attach targeting agents and active biomolecules using covalent bonds or electrostatic interactions such as hydrogen bonds.[162] They also have a large surface-to-volume ratio, which allows for chemical modification, enhances cellular uptake, protects drugs within the biological medium, and improves bioavailability.[163]

Metal NPs can be used as carriers and contrast agents for active or passive tumor cell targeting. In passive targeting, the NPs can accumulate in tumor sites through permeability and retention due to the poor lymphatic drainage and defective vasculature of tumors. Functionalizing the surface of NPs with hydrophilic moieties, such as PEG, can improve drug solubility, prevent macrophage uptake, and shield enzymatic degradation during in vivo studies.[164] Metal NPs can directly induce DNA damage and eliminate tumor cells, making them a promising tool for cancer treatment. By selectively targeting cancer cells and inducing DNA damage, metal NPs can trigger apoptosis or necrosis, release tumor antigens, and activate immune cells. They can also synergistically activate multiple pathways to trigger cell death mechanisms.[165] However, preparing a stable colloidal suspension of metal NPs remains challenging due to metal-metal aggregation caused by their high surface energy. Researchers have used stabilizers like polyvinylpyrrolidone and polyacrylic acid to form a surface layer on metal NPs to reduce particle accumulation and improve the stability of the colloidal mixture.[164] In addition, as a safe-by-design strategy to attenuate the intrinsic toxicity of some metal/metal oxide NPs, a superficial layer can be deposited on their surface, and these NPs have been capped by biocompatible natural compounds with a core-shell structure.[166]

Gold Nanocarriers (AuNCs)

Gold nanoparticles are emerging as promising agents for cancer therapy and are being investigated as drug carriers, photothermal agents, contrast agents, and radiosensitizers.[167,168] Additionally, they can easily attach to biomolecules through Au-S bonds, further increasing their utility in biomedical contexts.[169] Metal-based nanoparticles, particularly gold and silver nanoparticles, are being explored for their unique optical properties that can be harnessed for effective photothermal therapy. Gold nanoparticles, for example, can absorb near-infrared light to generate heat, leading to

localized tumor destruction while minimizing damage to surrounding healthy tissues. Recent advancements in nanoparticle engineering have significantly enhanced cancer treatment by enabling targeted drug delivery to cancer cells while protecting healthy tissues. Stimulus-responsive nanoparticles facilitate regulated drug release, ensuring precise action against tumors.[170] Gold nanoparticles are being used in gene therapy and photothermal treatment (PTT) to transfer nucleic acids into tumor cells, a potential frontier in molecular medicine for cancer treatment.[112] This method eliminates cancer cells while minimizing harm to healthy tissues, enhancing the effectiveness of treatment. DOX is a highly effective chemotherapy drug but has significant toxicity to organs like the kidneys, liver, and heart.[171] Lee et al examined the in vivo and in vitro anticancer activity of DOX-loaded DNA/Au NPs for ovarian cancer treatment. They evaluated the release of DOX from the DOX-DNA-Au NPs in different pH buffers. An initial burst release was observed within 5 hours, with a higher release in the acidic pH 5.6 compared to pH 7.4. The release of DOX continued to increase over 48 hours, reaching approximately 14.6% in the pH 7.5 buffer, which indicates the high stability of DOX-DNA-Au NPs and the possibility of pH-dependent cancer-targeting drug delivery. The cellular internalization of the NPs was investigated in ovarian cancer cell lines, demonstrating a high cellular permeability and successfully reaching the nuclei of the cancer cells. The DOX concentration increased with the treatment time with drug-loaded NPs, while the free DOX concentration remained constant. The in vivo ovarian anticancer activity in the mice model showed that the NPs significantly reduced tumor size compared to the control group and free DOX, and the tumor growth inhibition rate was about 2.5 times higher than that of free DOX. Furthermore, no accumulation of NPs in other organs was observed, indicating their successful distribution on tumor sites, inducing minimal side effects.[172] Tam et al's study reveals the potential of gold nanoparticles/PLA polymer nanospheres as a theranostic platform. Gold nanoparticles over 50 nm have significant potential in the near-infrared radiation (NIR) region for efficient clearance, while the 4 nm size, which was loaded into a polymeric nanocluster, leads to efficient renal clearance.[173] There is an opportunity to investigate different gold nanoparticle shapes for organ-specific distribution, and generating luminescent gold nanoparticles (L-AuNPs) with long life is an opportunity for biomedical applications.

Silver Nanocarriers (AgNCs)

Silver nanoparticles not only deliver drugs but also possess antimicrobial properties, reducing the risk of infections in cancer patients. Additionally, magnetic nanoparticles can be directed to tumor sites using external magnetic fields, enhancing targeting precision and improving the overall effectiveness of cancer therapies.[174,175] Gene carriers (Ag NPs) with a high affinity for binding genes provide a promising gene delivery system for treating various diseases, including cancer.[161] Erdemir et al studied the effects of selenic acid (SA) and pyruvic acid (PA)-loaded silver nanocarriers on the viability of CRC cells. The researchers generated Ag NPs ranging from 2.32 to 5.61 nm in size, Ag-SA NPs from 3.61 to 13.54 nm, and Ag-PA NPs from 78.82 to 295.3 nm, and a gradual increase in the cumulative release of SA and PA from NPs was observed over time. The anticancer properties evaluations on the CRC cell line showed that Ag-SA NPs inhibited cancer cell viability, while Ag-PA NPs were ineffective. Additionally, PA was not cytotoxic and increased the CRC cell proliferation, but SA increased the cytotoxicity of Ag NPs by 5.3 times and demonstrated visible signs of apoptotic death and necrotic death in the treated cell groups.[176]

Platinum Nanocarriers (PtNCs)

Platinum-based anticancer drugs (eg, CP) have been widely used as a standard chemotherapeutic cancer treatment for many years. However, some of these drugs, such as carboplatin, oxaliplatin, and nedaplatin, often come with severe systemic toxicity and can cause side effects.[177] Regarding this drawback, researchers have employed platinum-based NPs because they have the potential to accumulate at tumor sites and be absorbed by tumor cells, which makes them more effective and reduces the side effects.[178] New prodrugs based on platinum (IV) have also been developed to minimize off-target interactions and side effects on healthy cells.[179] These prodrugs are activated inside cancer cells, releasing cytotoxic platinum (II) drugs.[180] Hydrogels containing platinum NPs have also been explored for tumor treatment. For example, an injectable and degradable photo-thermal hydrogel encapsulated in a platinum NP dendrimer led to complete tumor regression. Another study developed a biodegradable hydrogel for co-delivery of antitumor agents, which demonstrated superior efficacy and minimized systemic side effects.[181,182] Recently, a two-layer fibrin-based

multicomponent gel was presented as a local drug delivery system that could effectively suppress residual tumor cells after tumor resection and prevent recurrence and metastases.[183]

Molybdenum Nanocarriers (MoNCs)

Molybdenum disulfide (MoS_2) is a promising functional material due to its tunable structure and exceptional physico-chemical properties. Due to its capacity for easy surface functionalization and high drug adsorption, MoS_2 is considered an ideal material for loading drugs. MoS_2 nanoflower structures have better encapsulation efficiency, making them ideal for chemotherapeutic drug loading. The intense light absorption of MoS_2 makes it a suitable carrier for photo-thermal and photodynamic therapeutic agents, and its different morphologies have shown promising results in controlled and targeted drug delivery, minimizing side effects and increasing therapeutic efficacy. While prior reviews mainly focused on the optical/thermal characteristics of photodynamic/photo-thermal therapy, the remarkable catalytic properties in cancer treatments are frequently disregarded.[184] For intense, Soltani et al utilized exfoliated molybdenum disulfide nano-sheets modified with N-isopropyl acrylamide/methyl methacrylate and glutamine conjugation, achieving a maximum DOX adsorption efficiency.[185]

Metal/Metalloid Oxide Nanocarriers

Metal oxide nanoparticles, such as ZnO,[186] SiO_2,[187] and TiO_2 nanoparticles, have gained attention in drug delivery due to their unique properties. Metal oxide nanoparticles can be quickly loaded with drugs, functionalized with target agents, and localized to diseased tissue. They have high stability and a tunable shape and can be engineered to the desired size.[188] They also have a negative surface charge, allowing further functionalization with different molecules.[189]

Zinc Oxide Nanoparticles (ZnO NPs)

ZnO nanoparticles, in particular, have been extensively studied for drug delivery and cancer diagnosis and treatment. Their small particle size allows for easy absorption by the human body, is cost-effective, non-toxic, and has a high drug-loading capacity.[190] They can also be programmed for controlled drug release and targeted delivery. The ability to synthesize ZnO nanoparticles into hollow nanotube-type structures makes them suitable for prolonged drug-release applications.[191] Gomaa et al conducted a study on a combined anti-tumor and anti-inflammatory approach using zinc oxide nanoparticles loaded with DOX and folic acid (FA). The drug-loaded nanoparticles showed a spherical structure with a size of 19–23 nm. In vitro assays showed that the treatment of Ehrlich ascites carcinoma (EAC) tumor cells with ZnO nanoparticles loaded with DOX and/or FA accelerated the growth inhibition of tumor cells in a dose-dependent manner compared to the cells treated with DOX.[192]

Silica Nanoparticles (SiO_2 NPs)

Silicon dioxide (SiO_2) -also known as silica- is an oxide of silicon that is recognized as a metalloid. Mesoporous silica nanoparticles, with their large pore sizes, diverse functionality, and biocompatibility, are ideal for creating synergistic nanoplatforms, serving as drug carriers and therapeutic agents in complementary chemotherapy.[193] Silica nanoparticles are being utilized in early cancer treatment through enhanced drug delivery and imaging techniques, encapsulated with various chemotherapeutic agents.[194] Application of these nanoparticles in imaging techniques like fluorescence and magnetic resonance imaging, providing high image resolution and real-time visualization of anatomical structures in the body, while also protecting drugs from degradation by enzymes, enhances solubility with the ability of controlled releases.[195] A recent study has focused on a specific formulation of mesoporous silica nanoparticles coated with polydopamine (PDA), containing umbelliprenin with anticancer properties. The nanocomplex exhibited cytotoxicity against MCF-7 carcinoma cells and induced programmed cell death while showing low cytotoxicity to normal cells, indicating its safety. The study also demonstrated the induction of apoptosis in MCF-7 cells through the up-regulation of specific genes and fluorescent staining. The promising results suggest that further preclinical studies should be conducted to evaluate the potential use of this formulation in cancer treatment.[196]

Titanium Oxide Nanoparticles (TiO_2 NPs)

Biocompatible TiO_2 nanoparticles are being explored for tumor targeting and delivery of anticancer drugs like DOX,

PTX, and platinum-based drugs (eg, CP) to the tumor site.[197] Kim et al developed an ultrasound-driven system containing TiO_2 nanoparticles to deliver DOX to tumor cells.[198] Faria et al designed a novel system based on ZnS-doped TiO_2 nanotubes to release 5-FU in physiologic conditions, which showed promising potential as an anticancer drug delivery system.[199] Another example is the successful loading of DOX on TiO_2 nanotubes through adsorption forces to develop an efficient pH-controlled release system for antitumor drug delivery.[200] Studies showed that biocompatible coatings can inhibit the release of titanium ions and reduce the toxic effects of TiO_2, thereby improving the performance of nanoparticles for drug release.[199,200] For example, Pulit-Prociak et al modified TiO_2 nanoparticles with GSH to release tadalafil, revealing an 82% decrease in active substance release compared to non-modified nanoparticles. The modified nanoparticles also enhanced Chinese hamster ovary cell (CHO) proliferation by over 60% and had a less cytotoxic effect by 37%. The materials showed satisfactory purity and surface morphology. The results of in vitro studies demonstrated that the modified TiO_2 nanoparticles have a great potential for being applied as a drug carrier.[201]

Iron Oxide-Based NPs

Iron oxide nanoparticles hold significant promise as tools for cancer diagnosis and drug delivery. In modern theragnostics, they are used in hyperthermia therapy, which involves raising the temperature of cancer cells to induce cell death.[202] Physicians utilize targeted delivery of iron oxide nanoparticles to tumor cells, enhancing the effectiveness of magnetic hyperthermia in destroying these cells. Additionally, iron nanoparticles are employed in regenerative medicine[203] for magnetic cell labeling and tracking, allowing for the monitoring of cancerous cells via magnetic resonance imaging (MRI).[204]

Carbon-Based Nanocarriers

Research on nanocarbons, such as carbon nanotubes (CNTs), graphene, fullerene, nanodiamonds, and carbon nanoparticles, has been booming in recent years, particularly for developing delivery vehicles for imaging agents and drugs.[205,206] These carbon-based nanomaterials have unique properties suitable for biological applications, including a high surface-to-volume ratio, thermal conductivity, rigid structural properties, and excellent biocompatibility. Accordingly, they can be used to deliver water-insoluble drugs, antigens, antibodies, and nucleic acids to cancerous cells. Another advantage is their ability to incorporate targeting and aromatic drugs via hydrophobic interactions or supramolecular π-π stacking, making them better suited to drug delivery platforms with enhanced loading capacity and sustained release ability.[207] Carbon-based nanomaterials can be functionalized either covalently or non-covalently to enhance their biocompatibility, and can be combined with other diagnostic and therapeutic components. Furthermore, their tunable pore structure allows for reasonable control over drug release.[205] Graphene, in particular, is an attractive candidate for drug delivery due to its large surface area, unique mechanical features, and easy functionalization.[207] Potassium-containing graphene oxide nanocarriers were employed by Tiwari et al for dual delivery of gefitinib and camptothecin (CPT) anticancer drugs, and a better release result was reported for dual delivery compared to single delivery of each drug.[208] CNTs also have exceptional chemical and physical characteristics that make them useful for drug delivery. Specifically, the large surface area of CNTs increases the interaction with biological material, and their high aspect ratio (width to height) provides excellent cell penetration. Besides, their conductivity facilitates the integration of muscular and nervous tissues.[209] CNTs can be easily functionalized to target specific cancer cell surface receptors. Unlike traditional drug delivery approaches, CNTs do not require solvents, which reduces the damage to healthy cells caused by the drug.[210] Yang et al showed that the functionalized single-walled CNTs (SWCNTs) as DOX carriers effectively treated MCF-7 cells, which suggests SWCNT-PEG-PEI reveals significant antitumor impact and drug delivery ability compared to CNT-COOH and CNT-PEG. Fluorescence-based studies and flow cytometry analyses indicate that SWCNT-PEG-PEI is more easily internalized, enhancing apoptosis and inducing tumor cell death due to its improved dispersibility and stronger affinity for cancer cells.[211] In a study by Carneiro et al, a novel targeting drug delivery system was developed using multi-walled carbon nanotubes (MWCNTs), incorporating digoxin and FA. The release study of digoxin and FA under biological and slightly acidified pH conditions indicated a constant and non-pH-dependent release for FA, while a significant increase in digoxin release upon a pH change was observed.[212] Carbon nanoparticles can also be used as biological agent carriers to enhance the therapeutic index at a tumor site. Alternatively, they can be combined with external stimuli, such as light, to induce irreversible physical damaging effects on cells. In a

study,[213] an intelligent theranostic platform was designed from an NIR-responsive core-shell hybrid nanocomposite using hyaluronic acid-PLA and hydrophobic carbon dots. This composite structure targets cancer cells that overexpress CD44 receptors and enables NIR-triggered chemo-phototherapy for tumors. Nicosia et al developed carbon nanodots modified with biotin and loaded with a high concentration of irinotecan for controlled release, imaging of MDA-MB231 and MCF-7 cancer cells, and their destruction through photothermal and chemotherapeutic methods. The results demonstrated that the developed system is a safe and promising theranostic complex for IG-PTT in breast cancer.[214] Mirrahimi et al designed a structure of graphene oxide linked to superparamagnetic iron oxides and AuNPs, and the phase change agent, 1-tetradecanol, for drug release. The synergistic effect of NIR absorption of graphene oxide, X-ray attenuation of AuNPs, MRI contrast of iron oxides, and thermosensitive properties made this platform very suitable for controlled drug release.[215] To overcome lysosomal degradation of RNAi, Wang et al introduced an amphiphilic fullerene derivative (C60-Dex-NH2) for siRNA delivery to cancer cells.[216] The results showed that the synthesized structure can cause lysosomal trapping and membrane disruption by producing controllable reactive oxygen species under visible light irradiation. In another study, CNT-loaded ginsenoside (a component of puffed ginseng with anti-cancer activities) showed promise as a potential therapeutic strategy for TNBC immunotherapy.[217]

Quantum Dot-Based Nanocarriers

QDs are semiconductor nanocrystals with unique optical, thermal, and electrical characteristics.[218] They are made of a few atoms and have been widely used in nanoparticulate DDS.[219] QDs have sharp fluorescence and high photo-stability, which makes them ideal for in vitro and in vivo studies of particle trafficking.[5] One of the main applications of QDs in cancer nanomedicine is targeted drug delivery. They can be modified with target ligands, such as antibodies or peptides, to enhance drug targeting and bioavailability in specific areas. QDs also improve drug stability, prolong in vivo circulation time, and strengthen drug distribution and metabolism.[209,219] Amraee et al developed a delivery system based on functionalized graphene QDs loaded with TAM anticancer drugs. Functionalizing with FA and methoxy PEG led to a better binding to folate-positive breast cancer cells and a longer lifetime, respectively. They reported a sustainable and continuous increase in drug release over time, such that 89% of the whole drug was released after 42 hours, being effective against MCF-7 breast cancer cells.[220] QDs are being utilized not only for their imaging capabilities but also as an innovative DDS. Their tunable optical properties enable precise tracking of drug distribution in vivo, which is critical for assessing treatment responses. Recent advancements include the development of QDs that can release drugs in response to specific stimuli, such as light or ultrasound, thus enhancing their therapeutic potential while minimizing side effects.[221,222] Additionally, bioconjugated QDs linked to targeting ligands improve specificity for cancer cells, enabling more effective targeted drug delivery and imaging.[223,224]

Exosomes and Their Role in Targeted Therapy

Exosomes are extracellular vesicles produced by cells that act as cell-to-cell short/long-range interaction regulators. They carry various molecules such as nucleic acids, proteins, lipids, and metabolites. These vesicles have unique characteristics that efficiently deliver therapeutic payloads to target cells.[225,226] They have low toxicity and immunogenicity and have been used to deliver therapeutic payloads such as siRNAs, immunological modulators, and chemotherapeutic medicines. They have shown promise in improving immunotherapy and suppressing immune function in cancer treatment. Exosomes have also demonstrated remarkable anticancer activity with reduced toxicity levels.[227] Besides their therapeutic applications, exosomes also hold promise for disease diagnosis and prognosis prediction. Due to their high concentration of tumor-derived components, such as DNA, RNA, proteins, and lipids, exosomes can serve as potential biomarkers for tumor detection.[227,228] Researchers have developed methods to modify exosomes for imaging, monitoring, and diagnostics, making them valuable tools in biomarker research.[229] Furthermore, exosomes have been used to profile miRNA expression, which can provide insights into extracellular vesicle-based biomarkers, miRNA function, and liquid biopsy.[230] Specific tumor-type-specific extracellular vesicles and particle proteins have been discovered, suggesting their potential use in diagnosing tumors of unknown sources.[231] Biosensors capable of detecting specific exosome miRNAs have also been developed for cancer diagnosis.[232] Yong et al developed a biocompatible drug carrier for targeted chemotherapy using exosome-biomimetic porous silicon nanoparticles (PSiNPs). After incubating

tumor cells with DOX-loaded PSiNPs, exosome-sheathed porous silicon nanoparticles (E-PSiNPs) were generated by tumor cells and showed enhanced tumor accumulation and penetration into deep tumor parenchyma (Figure 5). Their significant cellular uptake and cytotoxicity in bulk cancer cells and CSCs led to a significant anticancer activity as well as CSC reduction in tumor models.[233]

Molecularly Imprinted Nanoparticles

Molecularly imprinted polymers (MIPs) are classified as synthetic materials capable of binding to target molecules through their specific recognition sites.[234] These materials have high affinity and selectivity, making them useful in various applications. In nanotechnology, MIPs can be found in different forms, such as spherical NPs, nanorods, nanofibers, and nanofilms, while those smaller than 200 nm have gained attention in cancer treatment. Nano-MIPs have a high surface area to volume ratio, allowing for efficient binding of target molecules. They also have fast binding kinetics, excellent dispersion and processability, and can be easily functionalized and modified. Additionally, nano-MIPs

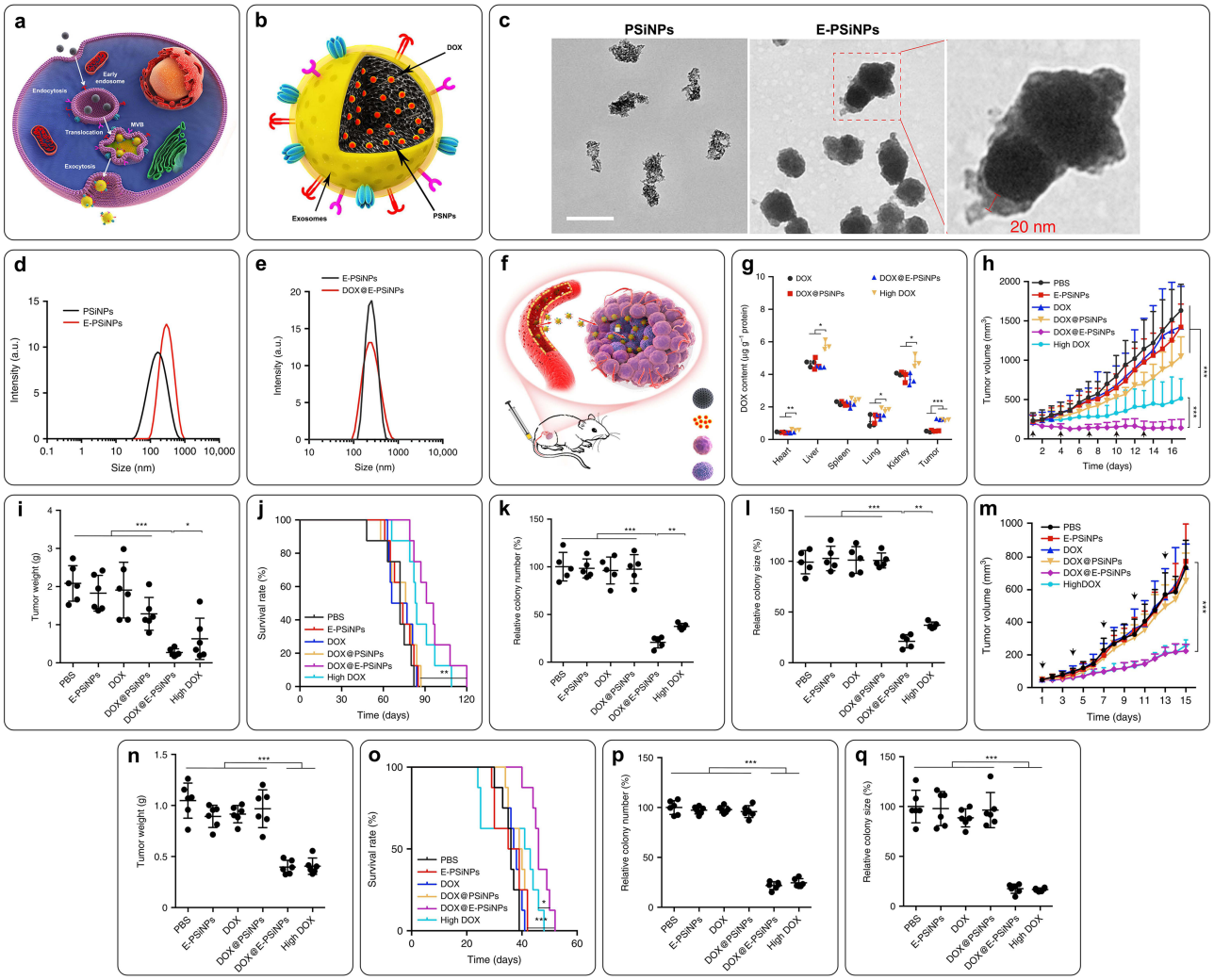

Figure 5 Schematic illustration of E-PSiNPs as drug carriers for targeted cancer chemotherapy. (**a**) Schematic illustration of the preparation of DOX@E-PSiNPs. After incubation, DOX@PSiNPs are endocytosed into cancer cells and localized in multivesicular bodies (MVBs) and autophagosomes. After MVBs or amphisomes fuse with the cell membrane, DOX@E-PSiNPs are exocytosed into extracellular space. (**b**) Schematics showing how DOX@E-PSiNPs efficiently target tumor cells after intravenous injection into tumor-bearing mice. (**c**) TEM images of PSiNPs and E-PSiNPs. Scale bar: 200 nm, (**d** and **e**) Hydrodynamic diameter of PsiNPs, E-PSiNPs, and DOX@E-PSiNPs by DLS analysis. (**f**) Schematic illustration of the efficient accumulation of DOX@E-PSiNPs in tumor tissues. (**g**) DOX content in tumor tissues and major organs of H22 tumor-bearing mice at 24 h after intravenous injection of DOX, DOX@PSiNPs or DOX@E-PSiNPs at DOX dosage of 0.5 mg kg^{-1}, or high dosage of DOX at 4 mg kg−1. (**h** and **l**) Anticancer activity of DOX@E-PSiNPs in H22 tumor-bearing mice (**h**) Tumor volume; (**i**) Tumor weight; (**j**) Survival rate %; (**k**) Relative colony number and (**l**) The size of tumor spheroids). (**m–q**) Anticancer activity of DOX@E-PSiNPs in orthotopic 4T1 tumor-bearing mice. (**m**) Tumor volume; (**n**) Tumor weight; (**o**) Survival rate %; (**p**) Relative colony number and (**q**) Size of tumor spheroids). *p*-values were considered significant at * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.[233]

are compatible with various medical devices and materials used in vivo.[234,235] Scientists have developed several synthetic approaches for nano-MIPs preparation, including emulsion polymerization, precipitation polymerization, solid phase imprinting, and surface imprinting.[236] Strategies like nano-precipitation imprinting, monomolecular imprinting, and self-assembly imprinting have also been developed but are less used nonetheless.[234,236] Li et al synthesized water-compatible hollow MIPs with hydrophilic polymer brushes on the surface, allowing for the delivery of drugs in aqueous environments.[237] Lu et al developed biodegradable silicon nanoparticles loaded with a model protein and modified with a sialic acid imprinting layer. These nano-MIPs targeted tumor cells, overexpressing sialic acid, and released the loaded protein to induce apoptosis.[238] Nano-MIPs have also been used in immunotherapy, and Gu et al developed anti-Programmed death-1 (PD-1) nano-MIPs that could block the PD-1/Programmed death ligand-1 (PD-L1) interaction, activating T-cell functions and reversing chemotherapy resistance in tumor cells.[239]

Hybrid Nanocarriers

Hybrid nano-vehicles, formed by combining two or more different NPs, offer numerous advantages, such as improved therapeutic efficacy, targeted delivery, reduced toxicity, and triggered release. The development of hybrid nanocarriers has revolutionized the drug delivery system by harnessing the combined effect of different components.[240] The current trend in the development of hybrid formulations allows for the synergy of beneficial properties from various systems, such as organic/inorganic, polymer/inorganic, lipid/inorganic, and lipid/polymer. This approach enables the design of nanocarriers with enhanced functionalities and tailored release profiles.[240–245] Hybrid nanoparticles are pharmacokinetically similar to drugs or small molecules and have shown great promise in cancer therapy through their efficient accumulation/retention at tumor sites, high penetration ability, and ability to carry/release chemotherapeutics in response to internal/external triggers.[246] One example of hybrid nanocarriers is the lipid-polymer hybrid (LPH) system, which combines the benefits of lipid-based carriers, such as better loading capacity and biomimetic nature, with the architectural benefits of polymeric carriers, acquiring desirable release profiles and targeting capabilities.[247] In a study by Rajana et al, FA-decorated palbociclib-loaded lipid/polymer hybrid NPs were fabricated using a quality-by-design approach. These hybrid NPs exhibited a uniform distribution with sustained drug release, and cellular uptake studies confirmed the uptake of nanoparticles by breast cancer cell lines.[248] In another study by Korganbayev et al, copper oxide nanoparticles were encapsulated in polymer nanospheres composed of PLGA and PDA/PEG. This theranostic nanosystem induced a photothermal response in the NIR range (808 nm) and increased temperature in tumors, making it a suitable construct for photothermal chemotherapies combined with diagnostic imaging for cancer treatment.[249] Liu et al synthesized a pH-responsive biocompatible hybrid polymer of Fe-Gallic acid hollow nanospheres with a combination of bovine serum albumin and DOX. This combination effectively responded to the TME in vitro and in vivo, releasing DOX and Fe (III) ions, which consumed GSH in cancer cells, generating Fe (II) for the Fenton reaction, which ultimately led to the generation of hydroxyl radicals for chemodynamic therapy. In addition, it effectively converted NIR light into heat as a therapeutic agent and enhanced the quality of MRI imaging.[250] Gao et al designed a mesoporous Fe-MIL-53-NH_2 nanomaterial as a carrier for the anticancer drug 5-FU and 5-carboxyfluorescein as a fluorescence imaging agent, as well as the targeting agent (FA). This transgenic metal-organic framework (MOF) showed excellent biocompatibility, high tumor uptake, significant anticancer effects, and good fluorescence and MRI imaging performance.[251] In another study, a surface modification by covalent bonding of FA and 5-carboxyfluorescein was performed on 5-FU-loaded UIO-66-NH2 nanoparticles (20–200 nm). These theranostic MOFs showed improved fluorescence imaging and enhanced antitumor efficacy due to sustained drug release.[252] Cherkasov et al synthesized a core-shell structure consisting of magnetic nanostructures carrying DOX and daunorubicin, and a polymeric outer surface linked with an antibody. The biocompatible nanoMOFs effectively carried therapeutic drugs at optimal concentrations and gradually released them near target cells.[253] Ni et al synthesized nanoscale hafnium-porphyrin-Fe MOFs and, with low-dose X-ray irradiation, they not only destroyed primary tumors but also suppressed distant tumors by activating systemic antitumor immunity.[254] To enhance radiotherapy and reduce the risk of postoperative recurrence, Chen et al synthesized and investigated FA-modified hafnium-based manganoporphyrin nanoMOFs.[255]

Smart Nanocarriers

Smart NPs are a promising option for cancer therapy because they can be triggered by specific stimuli and deliver drugs to targeted sites. Unlike conventional NPs, smart NPs can aggregate at the desired location and release their payload, resulting in a more precise and controlled treatment. This targeted drug delivery reduces the toxicity to healthy tissue and improves the effectiveness of cancer treatments.[256–258] Stimuli-responsive NDDSs are used to deliver therapeutic drugs to tumor sites without affecting surrounding areas. The advantages of such systems include reduced side effects, improved pharmacokinetics and pharmacodynamics, and controlled drug release.[259] They benefit from the EPR effect, which allows the nanocarriers to accumulate in the tumor.[260] Smart nanocarriers should possess specific characteristics such as not being eliminated by the body's immune system, accumulating only at the target site, releasing the cargo at the right concentration upon stimulation, and having the ability to co-deliver different substances such as chemotherapeutics, genetic materials, and imaging agents.[261] Stimuli-responsive NDDSs, by altering their physicochemical characteristics, intelligently respond to specific stimuli, either endogenous (ie, generated in the TME, such as pH, redox potential, overexpressed proteins, and enzymes) or exogenous (ie, applied from outside, such as light, ultrasound, magnetic, or thermal), which results in higher drug release through the EPR effect.[259]

Stimuli-Responsive Mechanisms

Endogenous Stimuli

Hypoxia in tumor cells produces reducing molecules like reductase and GSH,[262] which are crucial for maintaining intracellular redox balance.[259] The GSH level in the TME of tumor mesenchymal stem cells is around 0.5×10^{-3} M, indicating more extraordinary reduction conditions and hypoxia than normal or healthy cells.[263] This difference triggers the controlled release of redox-sensitive NDDSs.[262] Bu et al evaluated a redox-responsive alginate–ibuprofen derivative-based drug delivery system. They found that the release of DOX from the system was slow in a neutral pH environment but significantly increased in the presence of GSH, a reducing agent commonly found in tumor cells, which indicates the system can be triggered to release the drug in a tumor-specific environment.[264] Gupta et al studied redox-responsive NPs loaded with DOX and CUR. They observed that the release of both drugs was enhanced in the presence of GSH, leading to higher cumulative release rates and demonstrating the potential for dual drug delivery in CRC.[265] Liu et al developed self-assembled micelles for DOX delivery and showed that the cells could take up the micelles, and the drug could be released rapidly at the target site, enhancing the antitumor efficacy. This system was able to track the drug location and release it precisely at the tumor site.[266] The metabolic pathway of tumor cells differs from that of normal cells, leading to glycolysis and lactic acid production. However, abnormal blood vessel distribution and lymphatic reflux in tumor sites prevent timely lactic acid removal, resulting in acid accumulation and an acidic TME.[267] The pH of tumor tissue (mostly ranging from 6.5 to 7.2), which is lower than that of normal tissues, can act as a trigger for selective anticancer drug release.[268] The acidic conditions can lead to the protonation of functional groups, such as carboxylic acids.[269] This protonation increases the solubility and swelling of these polymers, which destabilizes the interactions between the drug and the polymer, allowing the encapsulated drugs to be released more easily.[270] Moreover, the acidic environment can also promote the hydrolysis of ester bonds within these polymeric carriers, further aiding in drug release. This mechanism enables a more targeted delivery of therapeutics directly to the tumor site, which helps minimize systemic exposure and reduces the risk of side effects.[271] Feng et al developed mesoporous silica nanocomposites for the delivery of bicalutamide. They found that the drug release rate could be regulated by altering the pH of the environment. This pH-responsive system showed promise as a carrier for anticancer drugs.[272] Enzyme-responsive DDS can also differentiate target sites from healthy tissues by utilizing active enzymes in the tissue.[273] Enzyme-sensitive carriers take advantage of the overexpression of certain enzymes in the TME to achieve targeted drug release. Candidate enzymes that act like molecular scissors, cleaving peptide linkers that hold the drugs within their carriers. When these linkers encounter higher concentrations of these enzymes, they undergo a process called hydrolysis, breaking down the peptide bonds.[274,275] As a result, the therapeutic agents are released in a controlled manner, allowing for targeted delivery right at the tumor site.[276] This approach not only enhances the effectiveness of the treatment but also helps reduce exposure to healthy tissues, minimizing potential side effects. However, variability in enzyme expression across different tumors and within tumor regions can lead to unpredictable drug release rates, complicating treatment strategies.[277] Additionally, similar enzymes

in healthy tissues raise concerns about off-target effects, resulting in unintended drug release and potential side effects.[278] Proteases are particularly interested in creating such novel systems due to their over-expression in infectious diseases like cancer and inflammation.[279] Since enzymes can catalyze chemical reactions under mild conditions, delivery approaches based on enzymatic-responsive nanomaterials and able to provide bio-specificity and selectivity can fulfil many therapeutic requirements. For instance, active tumor-targeting NPs integrated with site-specific enzyme-triggered moieties could enhance drug release at the tumor site, reduce uptake by non-targeted tissue, and improve targeting, permeability and drug accumulation time, which ultimately led to a better antitumor effect.[262] Hsu et al investigated targeting drug delivery carriers for breast cancer using GSH-sensitive nanoparticles. They found that the release of DOX from the nanoparticles was triggered by the presence of GSH, leading to cytotoxic activity against breast cancer cells.[280]

Exogenous Stimuli

Light-mediated therapy uses extrinsic activation to prevent nonspecific drug release, enabling on-demand therapies and diagnosis in specific locations. Nanotechnology advances have enabled nanomaterials, including metal-organic frameworks, for light-responsive targeted DDS.[281] Quazi et al designed a light-triggered delivery system containing AuNPs by entrapping a cancer-specific peptide drug (ie, Buforin IIb) within the DNA networks of a nanoscale DNA hydrogel. Irradiation of a 660 nm laser stimulated the flocculated AuNPs, which led to the denaturation of DNA hydrogel nanocomplexes and the release of the peptide drugs. Their results suggested this light-activated system's efficacy in the delivery of anticancer peptide drugs specifically to cancer cells, without cytotoxicity or harmful effects on standard cell lines.[282] Ultrasound waves have attracted researchers' attention to be used as external stimuli in target-controlled drug release systems, due to their safety, non-invasiveness, proper spatiotemporal control, and tissue penetration.[279] In this regard, important parameters such as sustained drug encapsulation, release performance in response to ultrasound waves, and release monitorability should be taken into account while designing such nanocarriers for therapeutic purposes.[283] In a study by Wang et al, nanobubbles carrying androgen receptor siRNA were investigated for their anti-tumor effects on androgen-independent prostate cancer. In vitro studies showed that when combined with ultrasonic irradiation, the nanobubbles significantly inhibited the growth of cancer cells and suppressed androgen receptor mRNA and protein expression. Contrast-enhanced ultrasound also demonstrated that the nanobubbles had stronger signals than the control in the tumor area.[284] Another study by Wang et al focused on ultrasound-responsive DDS for hepatocellular carcinoma. Ultrasound-induced structural destabilization accelerated the release rate of DOX payloads, leading to potent cytotoxic efficacy in affected cells.[285] Thermosensitive nanocarriers such as micelles, hydrogels, liposomes, and dendrimers are another stimuli-responsive delivery system with beneficial features, including high solubility, stability, longevity, and responsiveness to local changes.[273] Temperature plays a crucial role in cellular metabolism, and exposing pathological sites like tumor tissues to elevated temperatures induces hyperthermia. Heating tumor tissue increases pore size externally, blood flow, and perfusion, which enhances nanocarrier extravasation.[283] Some researchers have studied the potential of liposome-micelle-hybrid carriers to enhance the co-formulation and delivery of PTX and 5-FU. It was reported that the drug release was more pronounced at higher temperatures, and the release profile also varied depending on the carrier type. The hybrid nanocarrier also increased the permeability and transport of PTX across cell monolayers and enhanced cytotoxicity against cancer cells.[286] An effective system for dual delivery of DOX and carboplatin drugs to breast cancer cells, through a pH/temperature-sensitive core-shell nanoformulation has been developed. It was reported that the nanoformulation could effectively release the drugs in the acidic conditions and showed significant cellular uptake in the breast cancer cells.[287] An external magnetic field can be applied as an exogenous stimulus to control magnetic nanoparticles and enhance the function of anticancer drugs like DOX by enhancing reactive oxygen species production. Magnetic NPs are nanostructures ranging from 1–100 nm, usually with a central magnetic core and a surface functional coat.[288] They have been proposed for drug delivery since 1970, but their use in treating malignant tumors has recently gained attention.[289] The magnetic targeting approach allows for targeted drug release in tumor sites with reduced side effects, as well as monitorability of magnetic NPs using magnetic resonance imaging.[3,290] Iron oxide has been widely used as the central core of NPs due to their high magnetic susceptibility, low coercivity, Curie temperature, toxicity, and production costs.[291] In order to treat glioblastoma, Norouzi et al developed DOX nanocarriers based on magnetic iron oxide NPs, stabilized with trimethoxysilylpropyl-ethylenediamine triacetic acid (TMSEDTA). The NPs demonstrated a burst release of 42% within 3 hours, with the

remaining DOX gradually released over 4 days. The release was accelerated at pH 4.5, which is beneficial for targeting the glioma. The drug-loaded NPs could bypass the efflux system and showed enhanced cellular uptake and drug accumulation in tumor cells through the magnetic field in comparison with DOX alone.[292] In another study, magnetic-luminescent composite nanoparticles with a magnetic core of $CoFe_2O_4$ were designed for co-delivery of the anticancer drugs MTX and DOX in breast cancer cells. The nanocomposite carriers with sizes below 50 nm showed high loading efficiency for both drugs and released 100% of MTX and 97% of DOX payloads in a simulated cancerous tissue environment after 84 hours. The cells treated with the drug-loaded nanoparticles showed an increase in apoptotic cells, indicating an effective cancer cell targeting.[293] Hybrid nanoparticles, like PLGA hybrid nanoparticles, can also control the drug release using a remote radiofrequency field.[273,281] Table 1 shows the classification of nanocarriers with anticancer agents along with their effective parameters, while Table 2 provides a comparative overview of the advantages and disadvantages of nanocarriers in cancer therapy.

Integrating Immunotherapy with Nanocarrier Applications

Immunotherapy has emerged as a promising strategy for treating cancer due to its specificity in boosting the body's natural defense mechanism against cancer cells.[294] However, the conventional delivery of immunotherapeutic agents often leads to side effects and reduced patient compliance. Additionally, the tumor's immunosuppressive microenvironment limits the efficacy of immunotherapy. Nanotechnology offers a potential solution to these challenges and has the potential to revolutionize cancer immunotherapy. Nanoparticles have shown the ability to enhance the effectiveness of immunotherapeutic agents by targeting immunocytes and reprogramming the TME.[112] This approach improves the treatment outcomes of immunotherapy by enhancing the delivery of immunotherapeutic agents directly to the tumor site, minimizing systemic toxicity.[295] This treatment destroys tumor cells and prevents their recurrence by triggering a significant immune reaction against the tumor.[296] There are three essential factors for effective cancer immunotherapy: effective transfer of cancer antigens to immune cells (especially antigen-presenting cells), induction of an anti-cancer immune response, and modulation of the immune-suppressive TME. Nanotechnology can be used for each of these aspects and has the potential to induce anti-cancer immune responses effectively.[297] By altering the biophysical features of NPs and incorporating functional ligands, they can target specific cell types such as tumor cells, dendritic cells, T cells, or TME.[298] Nanoparticles can also incorporate multiple immunotherapeutic agents for cancer targeting or immune cell delivery. Co-delivery of immunotherapeutic agents within a single cell has been shown to enhance the immune response and optimize antigen processing and presentation.[299] The TME significantly influences drug penetration and efficacy, correlating with treatment resistance and diminished response rates. The modulation of the TME has garnered interest from researchers focused on cancer immunotherapy. Nanoparticles can extend retention duration and facilitate targeted distribution, hence minimizing toxicity. They can also change the immunosuppressive environment in the TME by targeting its significant components and transforming it into an immunosupportive state, thus promoting the efficacy of cancer immunotherapy. CAR-T therapy of acute lymphoblastic leukemia has shown limited efficacy in melanoma and non-small-cell lung cancer, with reported adverse events. Nanocarriers are increasingly being employed to enhance the delivery of immunotherapeutic agents, such as checkpoint inhibitors and cancer vaccines. By encapsulating these agents within nanoparticles, researchers can improve their stability and bioavailability while ensuring targeted delivery to tumor sites. For instance, nanoparticles that encapsulate immune checkpoint inhibitors enhance their stability and bioavailability, allowing for more effective targeting of tumors. Additionally, the use of nanoparticles to deliver cancer vaccines can stimulate a robust immune response, improving vaccine efficacy, for example, Meng et al highlighted that biomimetic nanoparticles can enhance the immunogenicity of dendritic cell (DC) vaccines, allowing for better antigen presentation and accumulation in lymph nodes.[300] Formulations that co-deliver immunoadjuvants alongside therapeutic agents further enhance the overall immune response against tumors, representing a promising strategy in cancer immunotherapy.[301] Nanoparticles also have the potential to overcome the limitations of current immunotherapies and improve treatment outcomes for various types of cancer.[302] Miao et al's study uses liposome-protamine-DNA nanoparticles to treat pancreatic cancer by encapsulating plasmids encoding PD-L1 and CXCL12 traps, effectively tuning immunosuppressive TME and facilitating T-cell infiltration.[303]

Table 1 Classification of Nanocarriers and Effective Parameters for Cancer Therapy

Material Base	Nanocarrier	Drug	Size (nm)	Target	Efficacy	Ref.
Lipid	Cationic liposome	Paclitaxel	183 ± 29.1	Lung cancer	Biocompatible, Improved PTX antitumor effect in human/mice, Greater tumor size reduction for MLV/SUV with PEG shell than PTX, protection from PTX-induced painful neuropathy.	[76]
	Solid lipid	Docetaxel	120	Breast cancer	>120 days stability, sustained release, Higher tumor cell cytotoxicity, Efficient cellular uptake, Inhibited 4T1 tumor growth prevented lung metastasis at 10 mg/kg.	[92]
Polymer	Methoxy PEG- poly(lactic acid)	Docetaxel	264.3 ± 7.28	Breast cancer	Sustained release, MCF-7 and MDA-MB-231 cytotoxicity in 2D culture, and MCF-7 cytotoxicity in 3D culture.	[111]
	Polymersome-based Kollicoat ®-poly(ε-caprolactone)	Co-delivery of Nisin and Curcumin	110 ± 1.03 nm	Breast Cancer	Controlled drug release for optimized polymersomes.	[144]
Protein	Bovine Serum Albumin	Plumbagin	186.60 ± 1.20	Breast cancer	Higher anticancer efficacy than pure PLB, Higher cytotoxicity/apoptotic effect than pure drugs, Increased internalization of PLB.	[148]
	Casein + $CaCl_2$ as a crosslinker	10-Hydroxy camptothecin	16 ± 3 nm	Highly metastatic TNBC cells	Sustained release, Excellent biocompatibility, Antimetastatic effects against TNBC, Anticancer activity by inducing ROS generation.	[149]
Metal	Silver	Paclitaxel	34.56 nm	MCF-7 (breast adenocarcinoma cell line), A549 (lung carcinoma cell line), C6 (brain glioma cell line) cells, and healthy WI-38 (fibroblast normal cell line) cell lines	Higher anticancer activity than PTX, Increased apoptosis by inducing DNA fragmentation, Antimicrobial activity against*A. baumannii, P. aeruginosa, S. aureus*, and Methicillin-resistant *S. aureus*).	[175]
	Au NPs (Oligonucleotide coated)	Doxorubicin	23.2 ± 4.8 nm	Colorectal cancer	>100 h structural stability, enhanced cellular permeability, Higher cellular uptake than free DOX, Enhanced cytotoxicity, Tumor growth inhibition.	[168]
Metal Oxide	ZnO	Cisplatin (Cp) and gemcitabine (Gem)	~20 nm	NSCLC	Higher A549 viability decrease than pure CP and Gem, Enhanced apoptosis effect of CP and Gem.	[186]
	Mesoporous silica	Doxorubicin hydrochloride	~ 25 nm	Colorectal cancer	Controlled release in normal tissues, Enhanced release under acidic conditions.	[187]
Carbon	Multiwalled carbon nanotubes (MWNTs)	Co-delivering sorafenib (Sor) and epidermal growth factor receptor (EGFR) siRNA	~50 nm	Liver cancer	Enhanced cellular uptake, Inhibited clone number and induced cell apoptosis, Higher antitumor effect than free SOR and siRNA, and MWCNTs/SOR.	[206]
Exosome	hUCBMSC derived exosome	Co-delivery of Docetaxel and miR-125a	232.50±12.9	Breast cancer	Higher cytotoxicity than free DTX, Facilitated cellular uptake.	[225]
	Platelet exosome	Doxorubicin	116 ± 3.73	Triple-negative breast cancer cells	More toxic effects than Dox (1 μg/mL), Facilitated DOX cellular uptake, Accelerated apoptosis.	[226]

(*Continued*)

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Table 1 (Continued).

Material Base	Nanocarrier	Drug	Size (nm)	Target	Efficacy	Ref.
Hybrid	LPH NPs solid lipid (Illipe butter) and chitosan	Solasonine/ solamargine	130.12 ± 9.03	Bladder cancer	Antiproliferative and cytotoxic effects on bladder cancer cells, Higher cytotoxicity than free glycoalkaloids, Antitumoral effects on bladder cancer model.	[242]
	Chitosan/Agarose/ TiO_2-carbon QDs	5-Fluorouracil	134.16	Brain Cancer	Lower cellular toxicity than pure 5-FU, Excellent stability in suspension, Compatibility, Extended half-life and reduced toxicity.	[243]
	FA-graphene QDs	Tamoxifen	20-40 nm	Breast Cancer	Elevated release rate under acidic conditions, Superior toxicity against MCF-7.	[244]
	Functionalized graphene oxide NPs	Quercetin (QUE) and curcumin (CUR)	30.26 nm	MDA-MB-231 cell line (human breast cancer cell line)	Higher cytotoxicity than pure drugs, Higher potency against MDA MB 231 cancer cells than pure drugs.	[245]
Smart	Multi-bioresponsive hyaluronic acid-geraniol NPs	Geraniol	138.5	Liver cancer	Promoted death of cancer cells, Sustained drug-release, Good stability, Simple and easy preparation.	[257]
	Carbon QDs/cyclodextrin-PEG-folate composite NPs	Camptothecin (CPT)	22.3 nm	MCF-7 cells	Considerable toxicity, IC50 value better than free drug on MCF-7 cell line, Slow release of chemotherapeutics from nanocarrier over 100 h, Significant drug encapsulation.	[258]

Table 2 Comparative Advantages and Disadvantages of Nanocarrier Types for Cancer Therapy

Type	Advantages	Disadvantages	Examples in Cancer Therapy
Lipid-Based (Liposomes)	Biocompatible, biodegradable, non-immunogenic; compatible with hydrophilic/hydrophobic drugs; low toxicity; extended release; large payload capacity; protects drugs from environment.	Possible carrier toxicity; challenges in large-scale production and stability.	Doxil® for breast/ovarian cancer; Vyxeos® for leukemia; PEGylated liposomes for prolonged circulation in glioblastoma.
Lipid-Based (Solid Lipid Nanoparticles)	Physiological compatibility; high drug encapsulation; stability at room/body temperature; shields drugs from degradation.	Potential instability in certain formulations; limited to certain lipid matrices.	Curcumin-loaded SLNs for pancreatic cancer; PTX/5-FU-loaded for liver cancer; SOR/superparamagnetic iron oxide co-loaded for HepG2 cells.
Lipid-Based (Nanoemulsions)	High drug solubilization; thermodynamic stability; long shelf life; rapid onset; non-toxic/non-irritant; easy application (foams, creams); enhanced skin penetration.	Thermodynamic instability in some mixtures; requires emulsifiers.	Fucoside-Lapachol NE for intravenous treatment; Toxoid-omega-3 NE for PPT2 cells; Catechin-extract NE for PC-3 cells; DTX-NE for A-549 cells.
Polymer-Based (Polymeric Nanoparticles)	Customizable (synthetic/natural polymers); targeted delivery; controlled/prolonged release; protects from degradation; crosses BBB; site-specific targeting; reduces side effects.	Potential aggregation; non-specific uptake if not functionalized; degradation byproducts in some cases.	PLGA NPs for colchicine/purpurin in cancer cells; NO-conjugate albumin for neurogenesis; LHRH-Ru complex for mitochondria targeting; PSP/TDNs@DOX for MDR breast/ovarian cancer.
Polymer-Based (Micelles)	Enhances solubility of hydrophobic drugs; extends circulation time; improves uptake; passive targeting via EPR; biocompatible; low toxicity; core-shell structure.	Limited to amphiphilic copolymers; potential disassembly in vivo.	(Manuscript truncated, but implies use in hydrophobic drug delivery for tumors).
Inorganic (Metal Nanoparticles)	High stability; targeting precision; imaging capabilities (eg, gold for theranostics); magnetic guidance (eg, iron oxide).	Potential toxicity (eg, accumulation); immune responses; clearance issues.	Silver-PTX for breast/lung/brain cancer; Gold-oligonucleotide-DOX for colorectal cancer; ZnO-Cp/Gem for NSCLC.
Inorganic (Metal Oxides)	Catalytic properties; drug loading; stimuli-responsive; imaging (eg, QDs).	Cytotoxicity; environmental concerns; size-dependent clearance.	Mesoporous silica-DOX for colorectal cancer; TiO2-carbon QDs-5-FU for brain cancer.
Inorganic (Carbon-Based)	High surface area; drug encapsulation; multifunctional (eg, theranostics); photothermal effects.	Pulmonary toxicity (CNTs); aggregation; biocompatibility issues.	MWCNTs-SOR/EGFR siRNA for liver cancer; Graphene oxide-QUE/CUR for breast cancer.
Organic (Exosomes)	Natural biocompatibility; targeted delivery; crosses biological barriers; low immunogenicity.	Scalability/production challenges; variability in isolation.	hUCBMSC-exo-DTX/miR-125a for breast cancer; Platelet-exo-DOX for TNBC.
Hybrid	Combines benefits of multiple types (eg, stability from inorganics + biocompatibility from organics); enhanced targeting; synergistic effects; multifunctional.	Complex synthesis; potential increased toxicity from components; higher costs.	LPH NPs (lipid-chitosan)-solasonine/solamargine for bladder cancer; Chitosan/agarose/TiO2-CQDs-5-FU for brain cancer; FA-graphene QDs-Tamoxifen for breast cancer.

Nanoparticle formulation significantly improves the local delivery of immunoadjuvants to peripheral lymphoid organs while limiting systemic distribution, enhancing their immunological activity, and reducing systemic immunotoxicity.[304] Additionally, nanoparticle-based delivery of antibodies effectively targets and activates antigen-presenting cells (APCs) and T cells, demonstrating clinical benefits in various tumors, including melanoma, non-small cell lung cancer, renal cancer, and Hodgkin's lymphoma.[305] Traditional nanomedicine faces challenges in tumor infiltration due to systemic and local barriers that limit the efficacy of antitumor treatments. In contrast, nanoparticles can be directed to immune cells in lymphoid organs or other immune sites, stimulating systemic antitumor immunity and bypassing significant barriers associated with direct tumor targeting. Immune cells can penetrate natural barriers, such as tumor vasculature and the BBB, which nanoparticles typically cannot access. This allows for potentially more effective therapeutic action through immune modulation.[306] Thus, nanocarrier-based immunotherapy offers a novel delivery approach that targets immune cells while also directly modulating tumors, leading to enhanced antitumor activity through multifaceted therapeutic mechanisms.

Challenges in Nanocarrier Development and Application

The field of nanomedicine, particularly in cancer treatment, is rapidly evolving, with approximately 2000 nano-formulations currently undergoing clinical trials. Despite this promising landscape, the journey from development to market is fraught with challenges, including high production costs, technological complexities, and failures in clinical translation.[307] As a result, only a limited number of the numerous developed nanomedicines have successfully reached commercialization. The intricate nature of these formulations means that even minor alterations in their production can significantly impact both their therapeutic efficacy and side effect profiles.[308] Furthermore, while nanomedicines can effectively target tumors through the EPR effect, they also tend to accumulate in other organs with fenestrated endothelium, such as the spleen and liver, leading to unique cytotoxic effects influenced by their physicochemical properties.[309] Research in nanotoxicology has highlighted the specific side effects of nanomedicines at various biological levels.[310] Common adverse effects often stem from immunological reactions due to the accumulation of nanoparticles in the spleen and liver, their foreign nature, and the generation of ROS.[311] To address these toxicity concerns, strategies such as modifying nanoparticle surfaces with targeting agents that bind to receptors overexpressed on cancer cells or targeting motifs of both cell-specific and tissue-specific are being explored in personalized medicine.[312] For example, albumin-based nanocarriers can leverage the EPR effect while also targeting glycoprotein gp60 receptors, enhancing their therapeutic potential.[313] Despite these advancements, significant hurdles remain for the clinical translation of nanomedicines. The complex synthesis and modification processes complicate the consistent and affordable manufacture of clinical-grade products. Moreover, treatment regimens must be personalized to optimize efficacy and minimize toxicity, which adds another layer of complexity. The safety of exogenously produced nanocarriers is also a concern, as the biohazards associated with nanoparticle formulations are not fully understood, particularly regarding chronic toxicity from repeated use. While the toxicology of certain elements, such as heavy metals, is well understood in bulk, nano-manipulation can alter their properties, potentially leading to biological toxicity. The toxicity of nanoparticles is influenced by various factors, including size, shape, composition, and surface modification, necessitating detailed investigations for each new nanoparticle. This requires case-by-case assessments for potential toxicity, which is labor-intensive and must be conducted across diverse patient populations. Therefore, identifying biomarkers linked to clinical responses and selecting suitable patients for treatment are essential to minimize health risks and maximize therapeutic benefits.

Beyond the general toxicological concerns, the biocompatibility and long-term safety profiles of nanocarriers are paramount for clinical translation. Different classes of nanocarriers elicit distinct biological responses depending on their composition, surface chemistry, and degradation pathways.[314,315] For instance, lipid-based nanoparticles, while generally biocompatible, can trigger complement activation and acute hypersensitivity reactions in some patients, particularly those with pre-existing immune sensitivities.[314] Polymeric nanoparticles, such as those made from PLGA, may induce oxidative stress and inflammatory responses in immune cells like macrophages, mainly when stabilizers or surfactants are used in their formulation.[315] Inorganic nanoparticles, including gold, silica, and iron oxide variants, pose risks of bioaccumulation and organ-specific toxicity, with surface modifications playing a critical role in mitigating these

effects.[311,316,317] Moreover, long-term exposure to specific nanomaterials may lead to unforeseen chronic toxicity, such as fibrosis or autoimmune reactions, which are not fully captured in short-term preclinical models. Immune responses, ranging from opsonization and rapid clearance by the mononuclear phagocyte system to more specific immunogenic reactions, also vary significantly across nanocarrier types and must be carefully evaluated to avoid adverse outcomes in clinical settings.[310,318]

Even beyond toxicity, nanocarriers face significant physiological barriers that limit their efficacy. Rapid clearance from circulation limits their therapeutic window, while prolonged circulation can lead to off-target accumulation.[319] A critical obstacle is the BBB, a selective membrane that restricts the entry of nanocarriers and their payloads into the central nervous system.[320] Upon reaching the tumor site, nanocarriers encounter the TME, characterized by hypoxia, acidity, and high interstitial fluid pressure, all of which can negatively impact nanocarrier performance. Additionally, cellular membranes limit entry into tumor cells, and intracellular barriers like endosomal entrapment impede cargo delivery to specific subcellular compartments. To overcome these, nanocarriers can be engineered with specific materials that respond to the intracellular environment.[22] For instance, Feng et al[321] developed iR@ZIF-8 nanocomposites using a zeolitic imidazolate framework (ZIF) that degrades in acidic endosomes, successfully delivering miRNA into the cytoplasm. Looking even further ahead, next-generation, swarm-strategy, nanocarriers aim to navigate these physiological hurdles actively. Such systems would require effective propulsion mechanisms (eg, magnetic or ultrasonic), precise control systems for targeting, and a stable power source for sustained operation within the body, representing a significant shift from passive delivery to active navigation.

In the near term, bio-inspired strategies provide a compelling approach to overcoming these barriers. Coating nanoparticles with cell membranes can enhance evasion, targeting, and uptake. Hu et al[322] created cancer cell membrane-coated nanoparticles (CCNPs) to evade immune recognition and enhance tumor targeting by mimicking cancer cell surface antigens, thereby facilitating homotypic targeting and improving cellular uptake. Similarly, Harris et al showed that coating nanoparticles with red blood cell membranes extended circulation time and reduced macrophage clearance, leading to greater accumulation in tumors.[323] In another study, Luk et al developed leukocyte membrane-coated nanocarriers, leveraging the homing ability of immune cells to target inflamed or cancerous tissues for improved delivery within the tumor microenvironment.[324] These strategies enhance biocompatibility, reduce immunogenicity, and improve delivery within the TME.

Translation is also hindered by manufacturing and economic challenges. Scaling up production requires overcoming hurdles in scalability, reproducibility, and navigating stringent regulatory approval processes. The high costs of research, development, manufacturing, and regulatory compliance further hinder widespread clinical adoption, particularly in cancer therapies.[325,326] Comprehensive assessments using advanced in vitro models and longitudinal in vivo studies are essential to understand these interactions and fully design safer nanotherapeutic platforms.

Iron oxide nanoparticles (IONPs) face significant challenges in their application for imaging and therapeutic delivery, primarily due to their inability to accumulate effectively at tumor sites.[327] Non-targeted nanoparticles often fail to reach sufficient concentrations in tumors, limiting their utility in clinical settings.[328] To address this issue, researchers propose the development of highly sensitive imaging probes that can conjugate large amounts of therapeutic agents, specifically targeting tumors. However, the size of antibodies relative to the surface area of IONPs presents a challenge in effectively linking them, which can impede the nanoparticles' penetration into target tissues and diminish their imaging and therapeutic efficacy.[329] Additionally, concerns regarding the safety and potential toxicity of IONPs, particularly in living organisms, further complicate their application.[330] Strategies to overcome these limitations include surface modifications to enhance stability and biocompatibility, as well as the creation of targeted delivery systems to improve specificity and minimize off-target effects. Ultimately, optimizing the formation of IONPs to control their size, shape, and surface properties is crucial for enhancing their application efficiency in medical application.[331] Gold nanocarriers, as one of the nanomaterials used in the field of cancer therapy, face significant challenges regarding biocompatibility and toxicity, influenced by variability in nanoparticle preparation that affects size, shape, and surface chemistry. Inadequate functionalization can lead to adverse biological interactions.[317] Surface modification with biocompatible materials (polymers or proteins) has been shown to increase stability, reduce nonspecific interactions, and improve overall biocompatibility.[332] Assessing the toxicity of silica nanoparticles presents significant challenges, particularly regarding their higher doses and

cumulative effects. While silica is generally considered safe, its nanoparticle form exhibits distinct biological behaviors, necessitating thorough biocompatibility evaluations.[316] The manufacturing process allows for precise control over particle size and shape, yet variations in physicochemical properties can influence biological interactions and cellular uptake. Therefore, managing these factors is crucial to ensure consistent and predictable therapeutic outcomes. Pulit-Prociak showed that modifying titanium nanoparticles could inhibit the release of titanium ions and decrease the toxicity of TiO_2 nanoparticles. By coating the nanoparticles with GSH and galactose, they demonstrated that the toxicity of the nanoparticles was reduced and therefore could be useful for drug delivery.[201,333] The integration of CNTs into patient care necessitates a comprehensive understanding of their biocompatibility and potential toxicity. Due to their fibrous structure, CNTs pose safety risks, including bioaccumulation that can lead to oxidative stress, inflammation, and cellular damage.[334] Therefore, evaluating their biocompatibility is crucial. To mitigate adverse effects, researchers employ surface modifications and functionalization techniques, alongside investigating the metabolism and excretion pathways of CNTs to ensure their safe application in theragnostics.[335] Evidence indicates that CNTs can adversely affect various organs, particularly the nervous system, lungs, and blood vessels, with implications for gene expression related to anxiety and depression.[336] Specific types, such as SWNTs, have been linked to increased inflammation and neurotoxicity, underscoring the importance of size in their biological impact. Despite these concerns, CNTs have demonstrated efficacy in animal models for tumor suppression and drug delivery (PTX), highlighting their therapeutic potential.[336] Understanding the pharmacokinetics of CNTs and their long-term biological effects is essential for developing the safety data required for clinical translation. While CNTs present promising applications in medicine, addressing their biocompatibility and toxicity challenges remains a priority to ensure safe and effective patient care.[337] In vivo studies on animals have been pivotal in evaluating the toxicity of QDs through acute and repeated-dose assessments (subacute, subchronic, or chronic), shedding light on their adsorption, distribution, metabolism, and excretion (ADME) as well as interactions with the immune system. However, researchers emphasize the need to minimize such testing due to ethical considerations.[338] While polymer coatings have been shown to mitigate toxicity, concerns remain regarding the long-term effects and potential systemic accumulation of QDs.[339] Additionally, the inherent rigidity of QDs poses challenges in drug conjugation, necessitating further investigation into optimal functional groups for effective binding.[340,341] Spherical liposomes used in nanotherapeutics have limitations such as instability and the potential for active agents to leak before reaching their target.[342] To enhance stability, researchers are optimizing lipid compositions, using stabilizing agents like sodium benzoate, and improving encapsulation technologies.[343] Polymeric nanoparticles offer several advantages, including biodegradability, biocompatibility, and the ability to carry both hydrophobic and hydrophilic drugs while allowing for controlled drug release. However, they also have limitations, such as self-aggregation, the use of toxic organic solvents in some preparation methods, and high synthesis costs.[344] Common solvents like dichloromethane and chloroform used in the solvent evaporation method can produce toxic nanospheres.[345] The toxicity of polymeric nanoparticles is significantly influenced by quantum-size effects, which are associated with oxidative stress, cytotoxicity, and genotoxicity. Notably, the use of slightly cytotoxic CH-polymer as a stabilizer markedly increased the cytotoxicity of PLGA nanoparticles in THP-1 macrophages, highlighting the critical role of nanoparticles stabilizers in determining the local toxicity of PLGA-based nanomedicine.[318] The size of nanocarriers is a key concern when it comes to PAMAM dendrimers. Dendrimers of generation 5 or lower can be effectively eliminated through the kidneys, while those of generation 6 and higher rely more on liver clearance.[346,347] Dendrimers sized between 4–10 nm can interact with cellular components and overcome the endocytosis barrier. However, higher-generation PAMAM dendrimers are often avoided due to their high costs and significant toxicity.[346] Cationic dendrimers have a strong binding capacity with nuclei and anionic compounds, aiding in cell internalization.[348] However, they face challenges like nonspecific binding to plasma proteins and rapid elimination by the reticuloendothelial system.[349] Additionally, their interaction with negatively charged cell membranes can destabilize biological membranes, leading to cell lysis and higher toxicity, especially at elevated doses.[350] For example, a study by Pryor et al found that cationic PAMAM generation 6 was significantly more toxic to embryonic zebrafish than both neutral and anionic PAMAM of the same generation at the same concentration.[351]

The development of theranostic agents as a novel method in cancer treatment presents several challenges, primarily due to the complexity of tumor biology, which results in variability in receptor expression among patients and within tumors. This variability complicates the selection of appropriate agents.[352,353] Additionally, creating new theranostic

agents necessitates rigorous testing for safety and efficacy, which is often lengthy and costly.[352,354] Regulatory barriers further impede the transition from research to clinical application.[352,355] Key considerations for clinical use include the biocompatibility and stability of these agents, particularly nanoparticles, which must effectively deliver therapeutics without harming healthy tissues.[356] Researchers are investigating multifunctional theranostic platforms that integrate imaging and therapy, showing promising outcomes.[357] Ongoing clinical trials are crucial for overcoming these challenges and validating the effectiveness of theranostics, which have the potential to enhance personalized cancer therapies and improve patient outcomes in precision medicine.[352,355,358]

Future Perspectives in Nanocarrier Development

The landscape of nanocarrier technology is evolving rapidly, bringing forth exciting innovations that promise to improve cancer therapies significantly. Immune-cell-derived extracellular vehicles (EVs) carry immune-associated molecules and can be re-appropriated to target cancers. CD8 T cell-derived EVs carry anti-tumor cargo and can cause localized inflammation, causing further immune infiltration, which can be exploited for cancer targeting. Engineering the immune cells to generate copious amounts of EV PD-1 to mediate a PD-1-PD-L1 interaction can work like immunotherapeutics and be an alternative to checkpoint inhibitors. One of the most transformative directions in this field is integrating personalized medicine into the design of nanocarriers. This approach aims to tailor treatments to individual patients by considering their unique genetic makeup, biomarkers, and other personal health factors. For instance, researchers are exploring the use of patient-derived exosomes as nanocarriers to deliver targeted therapeutic agents specifically designed for individual tumors.[304,359] This level of customization enhances treatment effectiveness and minimizes unwanted side effects, as seen in studies where exosomes have been used to deliver chemotherapeutics directly to triple-negative breast cancer cells, resulting in reduced systemic toxicity.[360] As these innovations unfold, we can anticipate several exciting clinical applications. One promising area is targeted gene therapy, where nanoparticles can deliver nucleic acids—such as siRNA or mRNA—directly to specific cancer cells. This targeted delivery can potentially correct genetic defects or silence oncogenes effectively. For instance, lipid nanoparticles have shown success in delivering mRNA vaccines for cancer immunotherapy,[361] such as the BNT162b2 vaccine developed for COVID-19,[362] which has implications for treating tumors by eliciting a robust immune response against melanoma cells. Furthermore, the role of nanocarriers in immunotherapy is expected to expand, particularly in enhancing the delivery of immune-modulating agents directly to the tumor microenvironment. By designing nanoparticles that co-deliver tumor antigens and adjuvants, researchers can stimulate a robust immune response, thereby improving the effectiveness of cancer vaccines like Sipuleucel-T for prostate cancer.[363] Another promising avenue is the advancement of combination therapies made possible by nanocarriers. By enabling the simultaneous delivery of multiple therapeutic agents—such as traditional chemotherapeutics, immunotherapeutics, and gene therapies—nanocarriers can enhance treatment efficacy and help overcome the challenges posed by drug resistance. A notable example is the use of lipid-polymer hybrid nanoparticles that effectively deliver both paclitaxel and immune checkpoint inhibitors like anti-PD-1 antibodies. Recent studies have demonstrated that this combination leads to improved tumor regression in preclinical models of non-small cell lung cancer, showcasing the potential for synergistic effects that result in better therapeutic outcomes.[364,365] Moreover, the development of smart nanocarriers that respond to specific stimuli—such as changes in pH, temperature, or enzymatic activity—holds great potential for enhancing the precision of drug delivery. These innovative carriers can be programmed to release their therapeutic payloads only when they encounter specific conditions within the tumor microenvironment. For example, pH-sensitive nanocarriers have been designed to release their contents in the acidic environment typical of tumors, significantly improving the therapeutic index of drugs like doxorubicin in breast cancer treatment.[366,367] Additionally, temperature-sensitive nanocarriers are being investigated for their ability to release drugs in response to the elevated temperatures often found in tumors, further enhancing localized treatment efficacy in models of prostate cancer.[366] However, the journey from laboratory to clinic is not without its challenges, particularly regarding regulatory considerations. The unique properties of nanocarriers necessitate a comprehensive understanding of their pharmacokinetics, biodistribution, and long-term safety profiles. Regulatory agencies, such as the FDA and EMA, are increasingly focused on the characterization of nanomaterials, requiring detailed data on their interactions with biological systems. This includes evaluating potential toxicity, immunogenicity, and environmental impact.[368] Consequently, researchers must

prioritize the development of standardized protocols to assess the safety and efficacy of nanocarriers, facilitating smoother regulatory approval processes.[368]

The development of nanosystems capable of delivering treatment and diagnostic imaging in a unified system (theranostic) enhances efficacy and reduces tumor resistance and microenvironmental challenges. The use of nanocarriers, especially polymeric-based NPs, gained more attention due to their various advantages, such as versatility, biocompatibility, biodegradability, drug release control, on-site delivery, and the presence of various natural and synthetic forms, such as polymer conjugate complexes, dendrimers, polymeric micelles, and polymeric nanospheres for intelligent theranostic systems. Diverse polymeric NPs can facilitate targeted gene and drug delivery, along with various imaging contrast enhancement agents, radiotherapy, PDT, and PTT. Research on polymers for disease treatment and diagnosis is growing, but theranostic nanosystems are still in their early stages. As an interdisciplinary field, progress is expected to accelerate, providing new therapeutic strategies in the future. To navigate the complexities of nanocarrier technology and ensure these advancements translate into clinical practice, continued collaboration among researchers, clinicians, and regulatory bodies will be essential. As we move forward, addressing challenges such as tumor heterogeneity, optimizing nanocarrier design, and ensuring patient safety will be critical. By integrating advanced materials, innovative design strategies, and robust clinical validation, we can pave the way for the next generation of nanocarrier-based therapies, ultimately improving patient outcomes in the ongoing battle against cancer. As we look to the future, it is crucial to continue research investment and conduct rigorous clinical trials to address the challenges that remain in this field. This includes refining nanocarrier designs, ensuring their safety and efficacy, and navigating the complex regulatory landscape. Successful integration of these technologies into everyday clinical practice will depend on strong collaboration among researchers, clinicians, and regulatory bodies to establish standardized protocols and guidelines.

Conclusion

Innovative approaches such as the use of nanocarriers, by significantly enhancing DDS, not only improve drug efficacy but also minimize the side effects often associated with traditional therapies. The unique properties of nanocarriers allow them to address some of the most difficult challenges in cancer treatment, such as drug resistance and systemic toxicity. With the ability to deliver drugs directly to the tumor site, nanocarriers enable more personalized treatment plans tailored to the specific needs of patients, ultimately leading to better clinical outcomes. By deepening our understanding of how these systems work and exploring their diverse applications, as well as utilizing combination approaches such as theranostics therapy, we can pave the way for more effective, personalized, and safer cancer treatments. These technologies have the potential to significantly improve the lives of patients facing the challenges of this complex disease and offer hope for a brighter future in cancer care.

Abbreviations

5-FU, Fluorouracil; ABC, ATP-binding cassette; ADME, Adsorption, distribution, metabolism, and excretion; AI, Artificial intelligence; Akt, Protein kinase B; AML, Acute myelogenous leukemia; AraC, Cytarabine; ATP, Adenosine triphosphate; BBB, Blood-brain barrier; BCL-2, B-cell leukemia/lymphoma 2; CXB, Celecoxib; circRNA, Circular RNA; Ce6, Chlorin e6; CMC, Critical micelle concentration; CME, Clathrin-mediated endocytosis; CML, Chronic myeloid leukemia; CNTs, Carbon nanotubes; CP, Cisplatin; CPT, Camptothecin; CRC, Colorectal cancer; CSCs, Cancer stem cells; CXB, Celecoxib; CYP, Cytochrome p450; DAS, Dasatinib; DDS, Drug delivery systems; DNMTs, DNA methyltransferases; DOX, Doxorubicin; DTX, Docetaxel; EAC, Ehrlich Ascites Carcinoma; EGFR, Epidermal growth factor receptor; EMT, Epithelial-mesenchymal transition; EPR, Enhanced permeability and retention; E-PSiNPs, Exosome-sheathed porous silicon nanoparticles; ER, Estrogen receptor; EVs, Extracellular vesicles; FA, Folic acid; GC, Gemcitabine; GSH, Glutathione; GST, Glutathione S-transferase; HAPs, Hypoxia-activated prodrugs; HAS, Human serum albumin; HU, Hydroxyurea; IONPs, Iron oxide nanoparticles; LBNCs, Lipid-based nanocarriers; LHRH, Luteinizing hormone-releasing hormone; lncRNA, Long non-coding RNA; LNPs, Lipid-based nanoparticles; LPH, Lipid-polymer hybrid; L-AuNPs, Luminescent gold nanoparticles; MDR, Multi-drug resistance; MIPs, Molecularly imprinted polymers; miRNA, MicroRNA; ML, Machine learning; MOF, Metal-organic framework; MPS, Mononuclear phagocyte system; mRNA, Messenger RNA; MSI, Microsatellite instability; MTX, Methotrexate;

MWCNTs, Multi-walled carbon nanotubes; NC, Nanocomplex; NCs, Nanocarriers; NDDS, Nanoscale drug delivery systems; NEs, Nanoemulsions; NF-κB, Nuclear factor kappa B; NIR, Near-infrared radiation; NO, Nitric oxide; NPs, Nanoparticles; NSCLC, Non-small cell lung cancer; PA, Pyruvic acid; PAMAM, Poly(amidoamine); PARP, Poly(ADP-ribose) polymerase; PDA, polydopamine; PDAC, Pancreatic ductal adenocarcinoma; PDT, Photodynamic therapy; PEG, Polyethylene glycol; PEI, Polyethylenimine; P-gp, Permeability-glycoprotein; PLGA, poly(lactic-co-glycolic acid); PMs, Polymeric micelles; PSiNPs, Porous silicon nanoparticles; PTT, Photothermal treatment; PTX, Paclitaxel; QDs, Quantum dots; RES, Reticuloendothelial system; ROS, Reactive oxygen species; SA, Selenic acid; siRNA, Small interfering RNA; SLC, Solute carrier; SLNPs, Solid lipid nanoparticles; SOR, Sorafenib; SPECT, Single-photon emission computed tomography; SWCNTs, Single-walled CNTs; TAM, Tamoxifen; TME, Tumor microenvironment; TMSEDTA, Trimethoxysilylpropyl-ethylenediamine triacetic acid; TMZ, Temozolomide; TNBC, Triple-negative breast cancer; UGT, UDP-glycosyltransferase.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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