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Targeted Drug Delivery Strategies for Cancer Therapy: A Review

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ABSTRACT: Cancer remains a major global health challenge and is one of the leading causes of morbidity and mortality worldwide. Conventional chemotherapy is widely used for cancer treatment; however, it often lacks specificity and can lead to severe systemic toxicity due to the non-selective distribution of anticancer drugs. These limitations highlight the need for advanced therapeutic approaches that can selectively target tumor cells while minimizing damage to healthy tissues. Targeted drug delivery systems have emerged as a promising strategy to improve the effectiveness and safety of cancer therapy[19,20]. Targeted delivery involves directing therapeutic agents specifically to cancerous tissues using specialized carriers or targeting ligands. This approach enhances drug accumulation at the tumor site and reduces off-target effects. Various targeting strategies, including passive targeting based on the enhanced permeability and retention (EPR) effect, active targeting [27] through ligand–receptor interactions, and stimuli-responsive systems triggered by internal or external factors, have been widely explored. Nanotechnology has played a significant role in the development of advanced carriers such as liposomes, polymeric nanoparticles, dendrimers, micelles, and lipid-based nanocarriers for efficient drug delivery[1,2].These systems improve drug solubility, stability, and bioavailability while allowing controlled and site-specific drug release. Despite significant progress, challenges such as biological barriers, variability in tumor microenvironment, and large-scale production remain. This review highlights the fundamental concepts, various targeting strategies, nanocarriers, and recent advancements in targeted drug delivery systems for cancer therapy, emphasizing their potential to improve therapeutic outcomes and reduce treatment-related toxicity.

INTRODUCTION

Cancer is one of the most serious health problems worldwide and continues to be a major cause of morbidity and mortality. It is characterized by uncontrolled cell growth, abnormal proliferation, and the ability of cancer cells to invade surrounding tissues and metastasize to distant organs. Conventional treatment approaches such as chemotherapy, radiotherapy, and surgery have been widely used to manage cancer. Among these methods, chemotherapy remains a primary therapeutic option for many types of cancer. However, traditional chemotherapy often lacks specificity and distributes anticancer drugs throughout the body, affecting both cancerous and healthy cells. This non-selective action frequently leads to severe side effects, reduced therapeutic efficiency, and the development of drug resistance.

In recent years, targeted drug delivery systems have gained significant attention as an advanced strategy for improving cancer treatment. These systems are designed to deliver therapeutic agents directly to tumor tissues while minimizing exposure to normal cells. By concentrating the drug at the diseased site, targeted delivery can enhance therapeutic efficacy and reduce systemic toxicity. Advances in nanotechnology and pharmaceutical sciences have enabled the development of various

nanoscale carriers such as liposomes, polymeric nanoparticles, dendrimers, micelles, and lipid-based nanocarriers for efficient drug transport[1,2,9].Targeted drug delivery strategies generally involve passive targeting, active targeting, and stimuli-responsive mechanisms. Passive targeting exploits the enhanced permeability and retention (EPR) effect present in tumour tissues, whereas active targeting utilizes ligands that specifically bind to receptors overexpressed on cancer cells[27]. Stimuli-responsive systems further allow controlled drug release in response to internal or external triggers. These innovative approaches hold great potential for improving the safety and effectiveness of anticancer therapies and represent a promising direction for future cancer treatment.

OVERVIEW OF CANCER AND CONVENTIONAL CHEMOTHERAPY

Cancer is a group of diseases in which cells grow and divide uncontrollably due to disturbances in normal cellular regulatory mechanisms. Under healthy conditions, cell growth and death are carefully controlled to maintain tissue balance. However, genetic alterations in certain genes can disrupt these regulatory pathways, leading to abnormal cell proliferation[25]. Over time, these abnormal cells may accumulate and form tumors that can invade nearby tissues and spread to distant parts of the body through the bloodstream or lymphatic system. This process, known as metastasis, is one of the major factors responsible for the severity and high mortality associated with cancer.

Several factors contribute to the development of cancer, including genetic mutations, exposure to carcinogenic chemicals, radiation, viral infections, and lifestyle-related influences such as smoking and poor diet. These factors can damage DNA and alter signaling pathways responsible for regulating cell growth, repair, and programmed cell death. As a result, cancer cells gain the ability to survive longer, multiply rapidly, and avoid natural defense mechanisms of the body.

Chemotherapy is one of the most widely used treatment methods for cancer and involves the administration of chemical agents that inhibit the growth and multiplication of cancer cells. These drugs act by targeting processes essential for cell division, such as DNA synthesis and mitotic activity. Chemotherapy may be used alone or in combination with other treatments like surgery or radiation therapy, depending on the type and stage of cancer.Despite its widespread use, conventional chemotherapy has several disadvantages. Most anticancer drugs do not selectively target tumor cells and therefore also affect normal rapidly dividing cells in the body. This lack of selectivity often results in undesirable side effects such as hair loss, gastrointestinal disturbances, fatigue, and suppression of the immune system[42]. Additionally, issues such as poor drug distribution, limited drug accumulation in tumor tissues, and the development of drug resistance can reduce treatment effectiveness. These challenges have driven the development of targeted drug delivery approaches that aim to improve therapeutic outcomes while reducing harmful effects on healthy tissues.

CONCEPT AND PRINCIPLES OF TARGETED DRUG DELIVERY

Targeted drug delivery is an advanced therapeutic approach designed to transport medications directly to specific tissues, cells, or organs affected by disease. In the context of cancer therapy, the primary goal of targeted drug delivery is to concentrate anticancer drugs at the tumor site while minimizing exposure to healthy tissues. This strategy improves therapeutic effectiveness and reduces the harmful side effects commonly associated with conventional chemotherapy. The development of targeted delivery systems has been greatly supported by advances in nanotechnology, biotechnology, and pharmaceutical sciences[19,20].The concept of targeted drug delivery is based on the use of specialized carriers or delivery vehicles that can transport drugs through the bloodstream and release them selectively at the intended site of action. These carriers may include liposomes, nanoparticles, polymeric micelles, dendrimers, and other nanoscale systems. In many cases, the surface of these carriers can be modified with specific ligands such as antibodies, peptides, or small molecules that recognize receptors present on the surface of cancer cells. This recognition allows the drug-loaded carriers to bind to tumor cells and facilitate drug entry through cellular uptake mechanisms.

Several fundamental principles govern the effectiveness of targeted drug delivery systems. One important principle is selectivity, which ensures that the therapeutic agent preferentially accumulates at the diseased site rather than distributing throughout the body. Another key principle is controlled and sustained release, which allows the drug to be released gradually over time to maintain effective therapeutic levels. Stability in the biological environment is also essential so that the carrier protects the drug from premature degradation or elimination before reaching the target site. Additionally, an ideal targeted delivery system should possess biocompatibility and minimal toxicity, ensuring that the carrier itself does not produce harmful biological effects.

By integrating these principles, targeted drug delivery systems aim to improve drug bioavailability, enhance therapeutic outcomes, and reduce systemic toxicity. As research in this field continues to advance, targeted delivery technologies are expected to play a crucial role in the development of safer and more effective treatments for cancer and other diseases.

TYPES OF TARGETING STRATEGIES

Targeting strategies are essential components of modern drug delivery systems, particularly in cancer therapy. These strategies are developed to ensure that therapeutic agents are delivered preferentially to tumor tissues while minimizing their distribution to normal cells. By improving the localization of drugs at the diseased site, targeted delivery approaches can increase treatment effectiveness and reduce harmful side effects. Based on the mechanism used to reach the target site, targeting strategies are generally categorized into passive targeting, active targeting, and stimuli-responsive targeting.

1. Passive Targeting

Passive targeting utilizes the unique structural and physiological characteristics of tumor tissues to achieve drug accumulation at the cancer site. One of the most important factors responsible for passive targeting is the enhanced permeability and retention (EPR) effect[32,33,36]. Tumor blood vessels are often irregular and contain large gaps between endothelial cells, which allow nanosized drug carriers to pass through the vessel walls and enter the tumor tissue more easily than normal tissues.

In addition to increased vascular permeability, tumor tissues usually have inefficient lymphatic drainage. This condition prevents the rapid removal of drug carriers once they enter the tumor region, allowing them to remain in the tumor for longer durations. As a result, drug-loaded nanoparticles such as liposomes, polymeric nanoparticles, and lipid-based carriers can accumulate within tumor tissues and gradually release the drug. Passive targeting does not rely on specific molecular recognition but rather depends on the physical properties of the drug carrier, including particle size, surface characteristics, and circulation time in the bloodstream.

2. Active Targeting

Active targeting involves modifying the surface of drug carriers with molecules that can specifically recognize and bind to receptors present on cancer cells. These molecules, commonly known as targeting ligands, help guide the drug carrier directly toward tumor cells. Once the ligand binds to its corresponding receptor on the cancer cell surface, the drug carrier may enter the cell through receptor-mediated endocytosis, leading to improved delivery of the therapeutic agent.

Various types of ligands have been explored for active targeting. These include antibodies, peptides, vitamins, carbohydrates, and nucleic acid–based molecules such as aptamers. Many cancer cells overexpress certain receptors compared to normal cells, which provides an opportunity for selective targeting. By attaching suitable ligands to drug carriers, researchers can enhance the specificity of drug delivery and improve the amount of drug that reaches the cancer cells[27].

3. Stimuli-Responsive Targeting

Stimuli-responsive targeting systems are designed to release drugs when exposed to specific conditions or triggers. These triggers may originate from the internal environment of the tumor or may be applied externally to control drug release. The main purpose of this approach is to ensure that the drug is released primarily at the tumor site rather than during circulation in the body.Internal triggers include factors such as changes in pH, enzyme levels, and redox conditions that are commonly found in tumor microenvironments. For example, many tumors exhibit a slightly acidic environment compared to normal tissues, which can activate pH-sensitive drug carriers to release their contents. External stimuli include temperature, magnetic fields, ultrasound, and light. These external signals can be applied in a controlled manner to initiate drug release from specially designed carriers. Stimuli-responsive systems therefore offer an additional level of control over drug delivery and have significant potential for improving the precision of cancer treatment.

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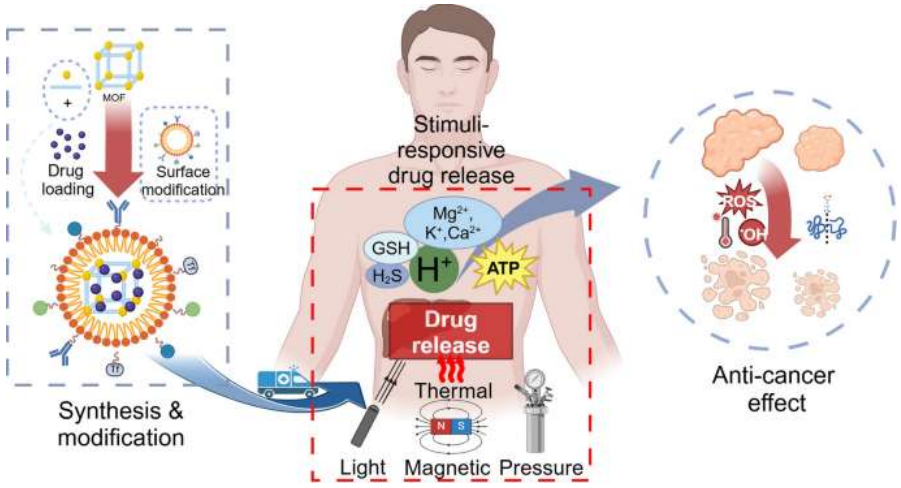

Figure-1 Stimuli-responsive drug delivery systems triggered by internal (pH, enzymes) and external (temperature, magnetic field, light) stimuli.[58]

TUMOR TARGETING MECHANISMS

Tumor targeting mechanisms describe the biological and physicochemical processes through which drug delivery systems preferentially accumulate in tumor tissues and interact with cancer cells. These mechanisms are fundamental for improving the therapeutic effectiveness of anticancer agents while minimizing damage to healthy tissues. Traditional chemotherapy often distributes drugs throughout the body, which leads to systemic toxicity and reduced treatment efficiency. In contrast, tumor-targeted delivery systems aim to concentrate the drug at the site of the tumor and enhance its uptake by malignant cells.

Targeting of tumors generally occurs at multiple levels. Initially, the drug carrier must accumulate within tumor tissue. After reaching the tumor region, the system should interact with specific molecular markers on cancer cells to facilitate cellular uptake. Finally, the therapeutic agent may need to reach specific intracellular compartments to exert its pharmacological action. Among the various mechanisms involved in tumor targeting, the enhanced permeability and retention effect, receptor-mediated targeting, and intracellular targeting are considered the most significant.

1. Enhanced Permeability and Retention (EPR) Effect

The enhanced permeability and retention (EPR) effect is one of the key mechanisms that enables passive accumulation of nanocarriers within tumor tissues. Rapid tumor growth requires the formation of new blood vessels through a process known as angiogenesis. However, the newly formed tumor vasculature is often poorly organized and structurally abnormal. The endothelial cells that line these blood vessels are loosely arranged, creating wide intercellular gaps that increase vascular permeability.

Because of these structural abnormalities, macromolecules and nanosized drug carriers ranging from approximately 10 to 200 nanometers can easily pass through the vascular walls and enter the tumor tissue. In contrast, normal blood vessels possess tightly arranged endothelial cells that restrict the passage of large particles. Another important factor contributing to the EPR effect is the inefficient lymphatic drainage in tumor tissues. In healthy tissues, the lymphatic system plays a crucial role in removing excess fluid and large molecules from the interstitial space. However, tumors often lack an effective lymphatic network, which prevents the rapid removal of drug carriers that accumulate in the tumor region. As a result, nanoparticles remain within the tumor for extended periods, allowing sustained drug release and increased therapeutic concentration at the target site[32,33].

Nanocarriers such as liposomes, polymeric nanoparticles, micelles, and dendrimers are commonly designed to take advantage of the EPR effect. Their size, surface properties, and circulation time in the bloodstream can be optimized to maximize tumor accumulation. Despite its advantages, the effectiveness of the EPR effect may vary depending on tumor type, location, and vascular characteristics.

2. Receptor-Mediated Targeting

Receptor-mediated targeting is an active targeting approach that enhances the specificity of drug delivery by utilizing molecular recognition between ligands and receptors. Many cancer cells overexpress certain receptors on their surface compared with normal cells. These receptors can serve as binding sites for specifically designed drug carriers.

In receptor-mediated targeting, the surface of nanoparticles or other drug carriers is modified with ligands that can recognize and bind selectively to these receptors. Commonly used ligands include monoclonal antibodies, peptides, vitamins, carbohydrates, and nucleic acid molecules such as aptamers. For example, folate receptors are frequently overexpressed in various types of cancer cells, making folic acid a widely used targeting ligand in anticancer drug delivery systems.

Once the ligand on the drug carrier binds to its corresponding receptor on the cancer cell surface, the carrier–receptor complex is internalized into the cell through a process called receptor-mediated endocytosis. This process significantly enhances the cellular uptake of the drug and increases the amount of therapeutic agent delivered to the tumor cells.

Receptor-mediated targeting not only improves the selectivity of drug delivery but also reduces the exposure of healthy tissues to cytotoxic drugs. This strategy has been widely explored in the development of targeted nanoparticles, antibody–drug conjugates, and ligand-modified liposomal formulations[27,35].

3. Intracellular Targeting

Intracellular targeting represents the final stage of targeted drug delivery, in which therapeutic agents are directed to specific locations within cancer cells. After a drug carrier enters the cell through endocytosis or other uptake mechanisms, the drug must often reach particular intracellular organelles to exert its pharmacological effect.

Different anticancer drugs act on different cellular components. For example, many chemotherapeutic agents target DNA within the nucleus, while others affect mitochondria, lysosomes, or cytoplasmic enzymes. Therefore, efficient drug delivery requires overcoming various intracellular barriers to ensure that the drug reaches the appropriate site of action.

One of the major challenges in intracellular delivery is the entrapment of drug carriers within endosomes after cellular uptake. If the drug remains trapped in these vesicles, it may be degraded before reaching its target. To overcome this limitation, advanced delivery systems are designed with mechanisms that allow endosomal escape, enabling the drug to enter the cytoplasm[30].Some drug carriers are also engineered with targeting signals or peptides that guide them toward specific organelles such as the nucleus or mitochondria. These specialized systems enhance the therapeutic effectiveness of anticancer drugs by ensuring that they interact directly with their intended intracellular targets.

Overall, intracellular targeting improves drug efficiency, enhances therapeutic response, and contributes to the development of more precise and effective cancer treatments.

NANOCARRIERS USED IN TARGETED DRUG DELIVERY

Nanocarriers play a crucial role in modern targeted drug delivery systems for cancer therapy. These nanoscale delivery vehicles are designed to transport therapeutic agents directly to tumor tissues while reducing exposure to healthy cells. Nanocarriers generally range in size from 1 to 200 nanometres and possess unique physicochemical properties that allow them to improve drug solubility, stability, and bioavailability. They also help protect drugs from premature degradation in the bloodstream and enable controlled or sustained drug release at the target site.

Another important advantage of nanocarriers is their ability to be modified with targeting ligands such as antibodies, peptides, or small molecules that recognize specific receptors on cancer cells. This modification enhances selective drug accumulation in tumor tissues and improves treatment efficiency. Various types of nanocarriers have been developed for targeted drug delivery, including lipid-based systems, polymeric carriers, and inorganic nanostructures.

1. Liposomes

Liposomes are one of the earliest and most widely studied nanocarriers used for drug delivery. They are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core. This structure allows liposomes to encapsulate both hydrophilic and hydrophobic drugs. Hydrophilic drugs are usually contained within the aqueous interior, while hydrophobic drugs are incorporated into the lipid bilayer.

Liposomes are highly biocompatible and biodegradable because their structure resembles natural biological membranes. These carriers can improve the pharmacokinetic properties of drugs by prolonging their circulation time in the bloodstream and reducing toxicity to healthy tissues. Liposomes can also be modified with polyethylene glycol (PEG) to create long-circulating or "stealth" liposomes that evade immune recognition. In targeted therapy, liposomes may be functionalized with ligands or antibodies to enhance selective delivery to tumor cells[1,3,4].

2. Polymeric Nanoparticles

Polymeric nanoparticles are solid colloidal particles prepared from biodegradable polymers such as poly lactic acid (PLA), poly lactic-co-glycolic acid (PLGA), chitosan, and polycaprolactone. These nanoparticles typically range from 10 to 1000 nanometers in size and can encapsulate drugs either within the polymer matrix or on the particle surface.

Polymeric nanoparticles offer several advantages, including controlled drug release, improved drug stability, and the ability to modify surface properties for targeted delivery. Their surface can be engineered to attach targeting ligands or protective coatings that improve circulation time in the body. Due to their versatility and ability to provide sustained drug release, polymeric nanoparticles have become widely used in cancer therapy and other biomedical applications[9,11].

3. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are lipid-based nanocarriers composed of lipids that remain solid at both room and body temperatures. These nanoparticles are typically stabilized by surfactants and have particle sizes ranging from approximately 50 to 1000 nm.

SLNs combine the advantages of traditional lipid systems with improved physical stability. They are capable of enhancing drug stability, protecting sensitive drugs from degradation, and providing controlled drug release. Additionally, solid lipid nanoparticles are generally well tolerated and biocompatible. Their lipid nature also allows them to interact efficiently with biological membranes, which can improve drug absorption and cellular uptake[5,7].

4. Nanostructured Lipid Carriers

Nanostructured lipid carriers (NLCs) are considered an advanced generation of lipid-based nanocarriers developed to overcome some of the limitations associated with solid lipid nanoparticles. NLCs consist of a mixture of solid and liquid lipids that form an imperfect lipid matrix.This modified structure creates additional space within the lipid matrix, allowing higher drug loading capacity and reducing the possibility of drug expulsion during storage. Nanostructured lipid carriers also provide improved stability and better control over drug release compared to conventional lipid nanoparticles. Because of these advantages, NLCs are increasingly explored for delivering anticancer drugs and other therapeutic agents[5,6].

5. Polymeric Micelles

Polymeric micelles are nanosized structures formed through the self-assembly of amphiphilic block copolymers in aqueous environments. These structures typically consist of a hydrophobic core surrounded by a hydrophilic outer shell. The hydrophobic core can encapsulate poorly soluble drugs, while the hydrophilic shell helps stabilize the micelle in biological fluids.

Polymeric micelles are particularly useful for improving the solubility and bioavailability of hydrophobic anticancer drugs. Their small size allows them to accumulate in tumor tissues through passive targeting mechanisms. In addition, the outer shell can be modified with targeting ligands to enhance selective interaction with cancer cells[38].

6. Dendrimers

Dendrimers are highly branched, tree-like polymeric molecules with a well-defined three-dimensional structure. They consist of a central core, repeated branching units, and multiple functional groups on the surface. This unique architecture allows dendrimers to carry drugs either within their internal cavities or attached to their surface.One of the major advantages of dendrimers is their high drug loading capacity and the ability to precisely control their size and structure during synthesis. Surface functional groups can also be modified with targeting ligands or imaging agents. Because of these characteristics, dendrimers are being investigated as multifunctional drug delivery platforms for targeted cancer therapy.

7. Carbon Nanotubes

Carbon nanotubes are cylindrical nanostructures composed of rolled sheets of carbon atoms arranged in a hexagonal pattern. They possess exceptional mechanical strength, electrical conductivity, and large surface area, which make them attractive for biomedical applications.

In drug delivery, carbon nanotubes can act as carriers for therapeutic agents through physical adsorption or chemical attachment. Their high surface area allows them to carry a significant amount of drug molecules. Additionally, they can be functionalized with various chemical groups to improve solubility and targeting ability. Although carbon nanotubes show great potential, concerns related to their toxicity and long-term safety still require further investigation.

8. Niosomes

Niosomes are vesicular nanocarriers formed by the self-assembly of non-ionic surfactants in an aqueous medium, often in combination with cholesterol or other stabilizing agents. Structurally, they resemble liposomes but are generally more stable and cost-effective.

Niosomes are capable of encapsulating both hydrophilic and hydrophobic drugs and protecting them from degradation. These carriers can improve drug bioavailability, prolong circulation time, and allow controlled drug release. In targeted drug delivery, the surface of niosomes can also be modified with ligands to enhance selective binding to cancer cells. Due to their stability, low toxicity, and ease of preparation, niosomes are increasingly studied as promising carriers for anticancer drug delivery systems[16].

LIGANDS USED FOR ACTIVE TARGETING

Active targeting is an important strategy in targeted drug delivery systems, particularly for cancer therapy. In this approach, drug carriers such as nanoparticles, liposomes, or micelles are modified with specific molecules known as ligands. These ligands have the ability to recognize and bind selectively to receptors that are overexpressed on the surface of cancer cells. The interaction between the ligand and its corresponding receptor enhances the accumulation of drug-loaded carriers at the tumor site and facilitates cellular uptake through receptor-mediated endocytosis. As a result, active targeting improves the specificity of drug delivery, increases therapeutic efficiency, and minimizes damage to normal tissues.

Different types of ligands have been explored for active targeting depending on the type of cancer and the receptors present on tumor cells. These ligands can vary in size, structure, and binding affinity, but they all serve the same purpose of guiding drug carriers toward specific biological targets. Some of the most commonly used ligands include antibodies, peptides, aptamers, vitamins such as folic acid, and proteins such as transferrin[27].

1. Antibodies

Antibodies are highly specific proteins capable of recognizing and binding to particular antigens present on cancer cell surfaces. Monoclonal antibodies are frequently used in targeted drug delivery because they can selectively bind to tumor-associated antigens. When antibodies are attached to drug carriers, they direct the carriers toward cancer cells expressing the corresponding antigen. This targeted interaction promotes receptor-mediated internalization of the drug carrier into the cancer cell, thereby enhancing therapeutic effectiveness. Antibody-based targeting has been widely applied in the development of antibody–drug conjugates and targeted nanoparticle systems[42].

2. Peptides

Peptides are short chains of amino acids that can be designed to recognize specific receptors on cancer cells. Compared with antibodies, peptides are smaller in size, easier to synthesize, and often show good tissue penetration. Many peptides have been identified that can bind selectively to receptors involved in tumor growth, angiogenesis, or cell adhesion. By attaching these peptides to nanocarriers, researchers can enhance the targeting capability of drug delivery systems and improve drug accumulation in tumor tissues[37].

3. Aptamers

Aptamers are short strands of single-stranded DNA or RNA that can fold into unique three-dimensional structures capable of binding specifically to target molecules. They function in a manner similar to antibodies but offer several

advantages such as lower immunogenicity, easier synthesis, and greater stability. Aptamers can be selected to bind to specific proteins expressed on cancer cells, making them useful ligands for targeted drug delivery. Their small size also allows them to penetrate tissues more efficiently and improve the delivery of therapeutic agents to tumor cells[45].

4. Folic Acid

Folic acid is one of the most widely used small-molecule ligands in cancer-targeted drug delivery. Many types of cancer cells overexpress folate receptors on their surfaces because they require large amounts of folate for rapid cell division. By attaching folic acid to the surface of drug carriers, the system can selectively bind to these receptors and enter cancer cells through receptor-mediated endocytosis. Folic acid is particularly attractive as a targeting ligand because it is small, stable, inexpensive, and easy to conjugate with drug carriers[27].

5. Transferrin

Transferrin is a natural iron-transporting protein present in the bloodstream. Cancer cells often express higher levels of transferrin receptors because they require increased iron for rapid growth and metabolic activity. Drug carriers conjugated with transferrin can bind to these receptors and be internalized into tumor cells. This targeting strategy enhances the delivery of anticancer drugs to malignant cells while reducing their interaction with normal tissues.

Overall, the use of targeting ligands significantly improves the specificity and effectiveness of targeted drug delivery systems. By selecting appropriate ligands that recognize tumor-specific receptors, researchers can design advanced drug delivery systems capable of providing more precise and efficient cancer treatment[35].

STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS

Stimuli-responsive drug delivery systems, often referred to as smart drug delivery systems, are advanced therapeutic platforms that release drugs in response to specific physical, chemical, or biological signals. These systems are designed to improve the precision of drug delivery by ensuring that the therapeutic agent is released only when it encounters a particular stimulus. In cancer therapy, such systems are highly valuable because they help concentrate the drug at the tumor site and reduce unwanted effects on normal tissues. Unlike conventional delivery methods, which release drugs continuously after administration, stimuli-responsive systems allow controlled and site-specific drug release.Stimuli used to activate these systems can originate either from the tumor environment itself or from external sources applied by clinicians. Internal stimuli include variations in pH, enzyme concentration, and redox potential that are commonly observed in tumor tissues. Tumors often exhibit a different biochemical environment compared with normal tissues due to altered metabolism and rapid cell growth. Drug carriers can be designed to respond to these internal conditions, leading to selective drug release within the tumor microenvironment.

External stimuli are signals that are applied outside the body to control the release of drugs. Examples include heat, magnetic fields, ultrasound, and light. In these systems, the drug carrier remains stable during circulation in the bloodstream and releases the drug only when the external stimulus is applied at the target location. This provides greater control over the timing and location of drug release.Materials used in stimuli-responsive systems are typically designed to undergo structural or chemical changes when exposed to a specific trigger. These changes may include degradation of the carrier matrix, alteration of particle structure, or breaking of chemical bonds that hold the drug within the carrier. As a result, the therapeutic agent is released in a controlled manner at the desired site[53].

Because of their ability to provide precise drug release and improved targeting, stimuli-responsive drug delivery systems are considered a promising strategy for enhancing the effectiveness and safety of cancer treatment. Continuous research in this area is contributing to the development of more sophisticated delivery systems capable of responding to multiple stimuli for improved therapeutic outcomes.

Different stimuli-responsive drug delivery systems are

1. pH -sensitive systems
2. Temperature- sensitive systems
3. Enzyme-responsive systems
4. Magnetic-responsive systems

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5. LIGHT-RESPONSIVE SYSTEMS

1. pH-Sensitive Drug Delivery Systems

pH-responsive systems are among the most widely studied stimuli-responsive drug delivery approaches. Tumor tissues and intracellular compartments such as endosomes and lysosomes generally exhibit a slightly acidic environment compared with normal physiological conditions. Drug carriers designed with pH-sensitive materials remain stable at neutral pH but undergo structural changes or degradation in acidic environments. This change triggers the release of the encapsulated drug specifically within tumor tissues or inside cancer cells. Polymers and lipids that respond to pH variations are commonly used to design such delivery systems.

2. Temperature-Sensitive Drug Delivery Systems

Temperature-responsive drug delivery systems release drugs when exposed to elevated temperatures. Tumor regions often exhibit slightly higher temperatures due to increased metabolic activity. Additionally, controlled heating techniques such as hyperthermia therapy can be used to increase the temperature of tumor tissues. Certain polymers and lipid materials undergo physical changes, such as phase transition or swelling, when the temperature reaches a specific threshold. This change leads to the release of the drug from the carrier at the target site.

3. Enzyme-Responsive Drug Delivery Systems

Enzyme-responsive drug delivery systems utilize the presence of specific enzymes that are found in higher concentrations in tumor tissues. Cancer cells often produce large amounts of enzymes such as proteases, esterases, or matrix metalloproteinases that are involved in tumor growth and tissue invasion. Drug carriers can be designed with enzyme-cleavable linkages that remain stable in normal conditions but break down when exposed to these enzymes. Once the linkage is cleaved, the drug is released directly in the tumor environment.

4. Magnetic-Responsive Drug Delivery Systems

Magnetic-responsive drug delivery systems involve the use of magnetic nanoparticles that can be guided to the tumor site using an external magnetic field. These particles are usually made of materials such as iron oxide. After administration, the magnetic field directs the drug-loaded nanoparticles toward the targeted region, improving drug accumulation at the tumor site. In some cases, alternating magnetic fields can also be used to trigger drug release or generate heat that enhances therapeutic effects.

5. Light-Responsive Drug Delivery Systems

Light-responsive systems use photosensitive materials that respond to specific wavelengths of light. When the targeted area is exposed to light, the photosensitive component of the drug carrier undergoes chemical or structural changes, resulting in drug release. This approach provides precise control over both the location and timing of drug delivery. Different types of light, including ultraviolet, visible, and near-infrared light, can be used depending on the design of the system. However, the limited ability of light to penetrate deep tissues may restrict its application in certain cases.

Applications table [31,34,41]

Application	Description
Targeted Chemotherapy	Targeted drug delivery systems improve the effectiveness of chemotherapeutic agents by directing them specifically to tumor tissues. Nanocarriers such as liposomes, nanoparticles, and micelles help concentrate drugs at the cancer site, which enhances therapeutic efficacy and reduces damage to healthy cells.
Gene Delivery in Cancer Therapy	Targeted carriers are used to deliver genetic materials such as DNA, siRNA, or mRNA to cancer cells. These systems help regulate or silence genes responsible for tumor growth, thereby inhibiting cancer progression and improving treatment outcomes.
Protein and Peptide Delivery	Therapeutic proteins and peptides can be delivered specifically to tumor cells using targeted nanocarriers. These carriers protect the biomolecules from degradation in the bloodstream and ensure their controlled release at the target site.

Application	Description
Photodynamic Therapy	Targeted drug delivery systems can transport photosensitizing agents to tumor tissues. When exposed to a specific wavelength of light, these agents produce reactive oxygen species that destroy cancer cells while minimizing damage to surrounding healthy tissues.
Combination Therapy	Targeted nanocarriers can simultaneously deliver multiple therapeutic agents, such as two chemotherapeutic drugs or a combination of chemotherapy and gene therapy. This approach enhances treatment effectiveness and helps overcome drug resistance.
Cancer Imaging and Diagnosis	Targeted drug delivery systems can carry imaging agents along with therapeutic drugs. These multifunctional systems allow visualization of tumor tissues and help monitor the effectiveness of treatment, supporting both diagnosis and therapy.
Immunotherapy	Targeted delivery systems are used to transport immune-modulating agents to tumor tissues or immune cells. This approach enhances the body's immune response against cancer cells and improves the effectiveness of immunotherapy treatments.

ADVANTAGES OF TARGETED DRUG DELIVERY SYSTEMS

Improved Drug Concentration at the Target Site

Targeted drug delivery systems help deliver therapeutic agents directly to the tumor or diseased tissue, increasing the concentration of the drug at the desired location and improving treatment effectiveness.

1. **Reduced Systemic Toxicity**

Since the drug is directed mainly to cancer cells, exposure of healthy tissues to toxic drugs is minimized. This helps reduce common side effects associated with conventional chemotherapy.

2. **Controlled and Sustained Drug Release**

These systems can be designed to release drugs gradually over time, maintaining therapeutic drug levels at the target site for an extended period.

3. **Enhanced Drug Stability**

Drug carriers protect the encapsulated drug from degradation or premature metabolism in the biological environment, ensuring that the active drug reaches the target site.

4. **Improved Bioavailability**

Targeted delivery systems can enhance the solubility and absorption of poorly soluble drugs, thereby improving their bioavailability and therapeutic effect.

5. **Reduced Drug Dosage**

Because the drug is concentrated at the disease site, smaller doses are often sufficient to achieve the desired therapeutic outcome.

6. **Minimized Drug Resistance**

By delivering drugs directly to tumor cells, targeted systems can help reduce the development of resistance that sometimes occurs with conventional therapies.

7. **Improved Therapeutic Efficiency**

The selective delivery of drugs enhances the overall effectiveness of treatment by ensuring that a greater amount of drug reaches the cancer cells.

8. **Protection of Sensitive Drugs**

Drug carriers can protect sensitive therapeutic agents such as proteins, peptides, and nucleic acids from degradation during circulation.

9. **Better Patient Compliance**

Controlled drug release and reduced dosing frequency make treatment more convenient for patients and improve adherence to therapy[40,41].

LIMITATIONS AND CHALLENGES OF TARGETED DRUG DELIVERY SYSTEMS

1. **Biological Barriers in the Body**

After administration, drug carriers must pass through several biological barriers such as blood circulation, immune defense mechanisms, and cellular membranes. The body's defense systems may recognize and eliminate these carriers before they reach the tumor site.

2. **Tumor Heterogeneity**

Cancer cells within the same tumor may have different biological characteristics. Not all tumor cells express the same receptors or molecular markers, which can reduce the effectiveness of targeted delivery systems that rely on specific receptor binding.

3. **Limited Penetration into Tumor Tissue**

Drug carriers that reach the tumor site may not easily penetrate deep into the tumor mass. Factors such as dense tumor structure, abnormal blood vessels, and high internal pressure within tumors can restrict drug distribution.

4. **Premature Drug Release**

Some drug delivery systems may release the drug before reaching the target site. This early leakage can reduce therapeutic efficiency and may cause unwanted side effects.

5. **Stability Issues**

Certain nanocarriers may face problems related to physical or chemical stability during storage or while circulating in the bloodstream, which can affect their performance.

6. **Complex Formulation and Manufacturing**

Developing targeted drug delivery systems often involves complex preparation techniques, specialized materials, and advanced technologies. This complexity can make large-scale production difficult.

7. **High Development Cost**

The research, development, and manufacturing of targeted drug delivery systems require significant financial investment, which may increase the overall cost of treatment.

8. **Potential Toxicity of Nanomaterials**

Some nanocarriers may accumulate in certain organs and could cause long-term toxicity or immune reactions. Therefore, careful evaluation of safety and biocompatibility is necessary.

9. **Regulatory Challenges**

Targeted drug delivery systems must undergo extensive safety and efficacy testing before clinical approval. Strict regulatory requirements can slow down the development and commercialization of these systems.

10. **Difficulty in Clinical Translation**

Many targeted drug delivery systems show promising results in laboratory studies but face challenges when applied in real clinical settings due to differences in biological environments and patient variability.

RECENT ADVANCES IN TARGETED CANCER THERAPY

Recent progress in cancer research has led to significant improvements in targeted cancer therapy. Advances in molecular biology, nanotechnology, and biotechnology have enabled the development of treatment strategies that specifically target cancer cells while minimizing damage to healthy tissues. These modern approaches focus on identifying molecular markers or receptors that are overexpressed in tumor cells and designing therapies that selectively interact with these targets.

One important advancement is the development of antibody–drug conjugates (ADCs)[20,42]. These systems combine monoclonal antibodies with potent anticancer drugs through specialized linkers. The antibody component recognizes specific antigens present on the surface of cancer cells and delivers the drug directly to the tumor, thereby increasing therapeutic effectiveness and reducing systemic toxicity.

Nanotechnology-based drug delivery systems have also gained considerable attention in recent years. Nanocarriers such as liposomes, polymeric nanoparticles, micelles, and dendrimers can transport anticancer drugs efficiently to tumor tissues. These carriers improve drug solubility, stability, and bioavailability while allowing controlled and targeted drug release[2,14].

Another significant development is cancer immunotherapy, particularly chimeric antigen receptor T-cell (CAR-T) therapy[25]. In this approach, a patient's immune cells are genetically modified to recognize and attack cancer cells. This method has shown promising results, especially in the treatment of certain blood cancers.

In addition, personalized medicine has emerged as an important strategy in targeted cancer therapy. By analyzing the genetic profile of tumors, treatments can be tailored to the individual patient, improving therapeutic outcomes. Overall, these recent advances are contributing to more precise, effective, and safer approaches for cancer treatment.

FUTURE PERSPECTIVES IN TARGETED CANCER THERAPY

Targeted drug delivery systems have shown great potential in improving the effectiveness of cancer treatment; however, continuous research is required to further enhance their clinical application. Future developments in this field are expected to focus on designing more precise and multifunctional delivery systems that can overcome current limitations such as poor tumor penetration, biological barriers, and variability in tumor characteristics. Advances in nanotechnology, biotechnology, and molecular medicine are likely to play an important role in the development of next-generation targeted therapies.

One promising direction is the development of multifunctional nanocarriers capable of performing several functions simultaneously, such as drug delivery, imaging, and real-time monitoring of treatment. These integrated systems, often referred to as theranostic platforms, may allow clinicians to diagnose tumors, deliver therapeutic agents, and evaluate treatment responses using a single system.

Another important area of future research is personalized or precision medicine. With improvements in genomic and proteomic technologies, it is becoming possible to identify the specific genetic and molecular features of individual tumors. This information can help design targeted therapies that are tailored to each patient, thereby improving treatment outcomes and reducing unnecessary drug exposure.

Researchers are also focusing on the development of smart drug delivery systems that can respond to multiple stimuli within the tumor microenvironment. Such systems may release drugs only when exposed to specific conditions such as changes in pH, enzyme activity, or temperature, allowing more precise control over drug release[17,20,22].

In addition, the integration of artificial intelligence and advanced computational tools is expected to accelerate drug discovery and optimize targeted delivery strategies. Overall, continued advancements in science and technology are likely to make targeted cancer therapy more effective, safer, and widely accessible in the future.

CONCLUSION

Targeted drug delivery has emerged as a promising approach in modern cancer therapy by addressing many of the limitations associated with conventional treatment methods. Traditional chemotherapy often lacks selectivity and can cause significant damage to healthy tissues, leading to severe side effects. In contrast, targeted drug delivery systems are designed to transport therapeutic agents directly to tumor tissues or cancer cells, thereby improving treatment efficiency while minimizing systemic toxicity. Various targeting strategies, including passive targeting, active targeting, and stimuli-responsive

delivery systems, have been explored to enhance the precision of drug delivery. In addition, different nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, micelles, and lipid-based systems have been developed to improve drug stability, bioavailability, and controlled release. The use of specific ligands and receptor-mediated mechanisms further enhances the selectivity of these systems toward cancer cells. Despite these advantages, certain challenges such as biological barriers, tumor heterogeneity, limited tumor penetration, and large-scale manufacturing difficulties still remain. Continuous research and technological advancements are therefore essential to overcome these limitations and improve the clinical success of targeted therapies. Recent developments in nanotechnology, immunotherapy, and personalized medicine are opening new possibilities for more precise and effective cancer treatment. Overall, targeted drug delivery systems represent an important advancement in oncology and hold great potential for improving therapeutic outcomes and patient quality of life in the future[19,20].

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