GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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Targeted drug delivery system for cancer and different diseases

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GSC Biological and Pharmaceutical Sciences, 2025, 30(03), 146-153

Publication history: Received on 28 January 2025; revised on 07 March 2025; accepted on 09 March 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.30.3.0101

Abstract

Targeted drug delivery systems have emerged as a promising approach for treating various diseases, including cancer, renal tubulointerstitial diseases, osteoarthritis, veterinary infections, cardiovascular disease, and asthma. These systems utilize nanoparticles, liposomes, or dry powder inhalers to deliver medications directly to the target site, minimizing systemic absorption and reducing side effects. Researchers have developed various targeting strategies, including kinase inhibitors, tyrosine kinase inhibitors, monoclonal antibodies, vascular targeted agents, and microtubules destabilizing target agents. Future studies should focus on developing more accurate targeting techniques and identifying new molecules for targeted delivery.

Keywords: Targeted drug delivery; Cancer treatment; Nanoparticles; Liposomes; Monoclonal antibodies

1. Introduction

Cancer arises from genetic or epigenetic alterations in somatic cells, leading to abnormal cell growth that can spread to other body parts. It's a subset of neoplasms, characterized by unregulated cell growth forming lumps or masses, potentially spreading diffusely [1]. With over 200 distinct types affecting 60+ human body organs, cancer is a leading global cause of death. Developing anti-cancer drugs poses a challenge in targeting cancer cells selectively and specifically [2].

One cutting-edge treatment, targeted drug therapy, offers high efficiency and minimal side effects, yet faces drawbacks such as limited druggable targets and patient population coverage, along with challenges in addressing drug resistance [3,4]. Understanding cancer's molecular mechanisms involves modeling interactome data into network structures, depicting biological entities and their associations, aiding in deciphering cancer genesis [5,6,7].

Targeted drug delivery is also known as smart drug delivery [8]. Targeted cancer therapies, also known as molecularly targeted drugs or precision medicines, interfere with growth molecules to inhibit cancer growth and spread [9]. Tumor initiation and progression involve a diverse range of cells and signaling mechanisms interacting with cancerous cells, making it an area of interest for effective cancer therapy research [10].

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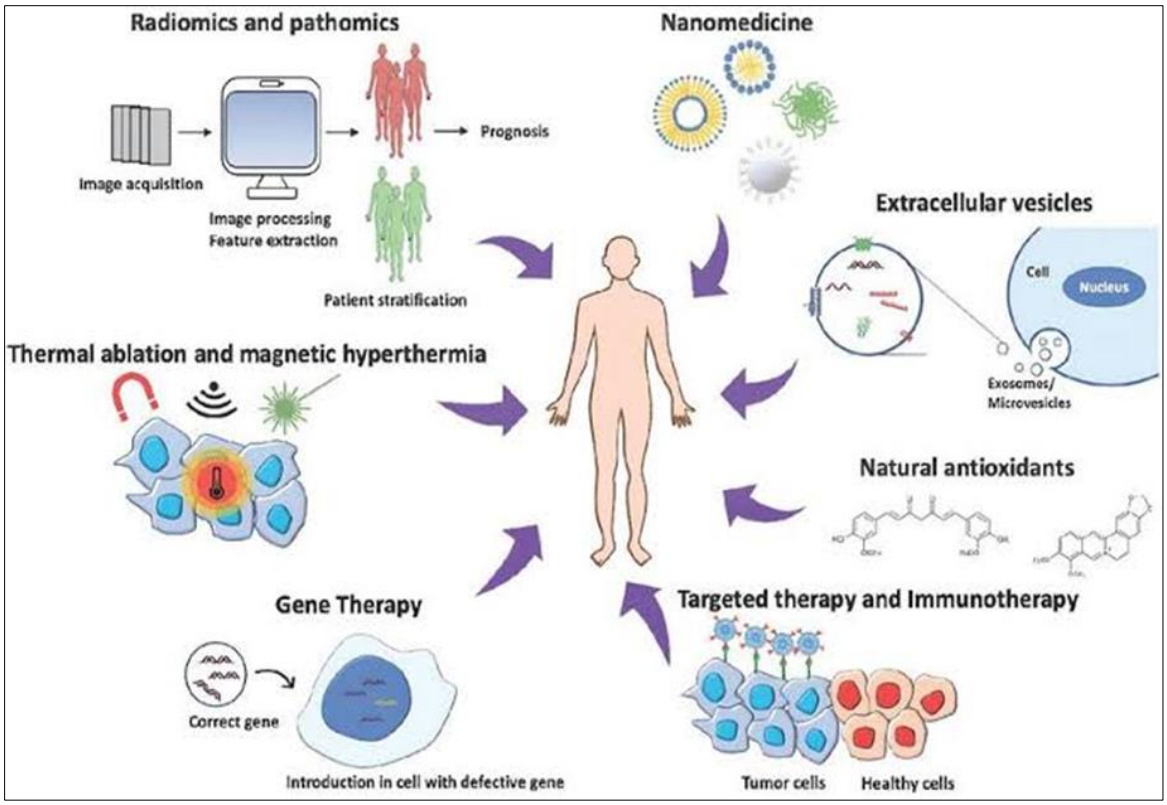

Figure 1 Cancer therapy approaches: The image represents the most innovative strategies to treat cancer, combining different disciplines to obtain the Most efficient and personalized therapy for patients [11]

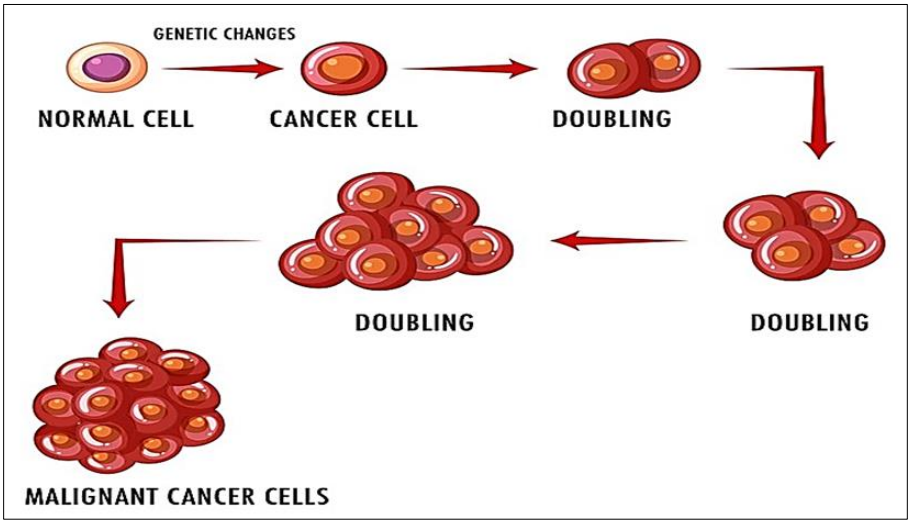

Figure 2 Cancer cell development process [12]

2. Targeted drug delivery system

Conventional chemotherapy struggles with selectivity due to its similarity to normal cells, prompting interventions through cellular mechanisms: Cell cycle arrest, inducing apoptosis, preventing proliferation, and interfering with metabolic reprogramming using targeted drug therapy agents [13]. Two strategies modifying the tumor microenvironment (TM) and targeting it for drug delivery are effective approaches in cancer treatment [14]. Targeted therapy drugs function differently from standard chemotherapy by attacking cancer cells while minimizing damage to normal cells, a unique programming that distinguishes them from healthy cells [15].

2.1. Kinase as target agents

Kinases act by transferring phosphate groups to proteins, while phosphatases remove phosphate groups, collectively regulating various protein activities in response to external stimuli [16]. Phosphorylation, stemming from these actions, can induce conformational changes that fine-tune biological networks and biochemical functions. Dysregulated kinase signaling plays a role in cancer hallmarks, with oncogenic transformations linked to amplification, genomic rearrangements, gain-of-function mutations, kinase gene deletions or dysregulated upstream kinase signaling [17].

2.2. Tyrosine kinase agents

Receptor Tyrosine Kinases (RTKs) exhibit common traits, including dimerization post-ligand binding and auto-phosphorylation of tyrosine residues. Ligand binding to RTKs extracellular domains activates the enzyme. This triggers a dynamic conformational shift in the monomeric receptor, leading to homo-/hetero-dimer formation and tyrosine kinase activity. Auto-phosphorylation occurs in the kinase domain and C-terminal region, prompting the assembly of signaling molecules harboring Src homology 2 and phosphotyrosine-binding domains. These molecules encompass kinases (e.g., PI3K, SRC), adaptor proteins (e.g., SHC, GRB2), transcription factors (e.g., STAT), ubiquitin ligases, and phospholipases (e.g., PLC-γ). They activate downstream signaling cascades, such as RAS/RAF/MAP kinase, PI3K/AKT/mTOR, PLC-γ/PKC, and JAK/STAT pathways. These pathways collectively induce diverse biological responses, including cell growth, survival, inhibition of apoptosis, promotion of angiogenesis, and activation of cell motility [18].

2.3. Monoclonal antibodies

Antibody drugs, synthetic versions of immune system proteins, are intravenously administered to target specific molecules on cancer cells. They comprise a higher proportion of human components than murine ones. Their mechanisms involve recruiting host immune functions to attack target cells, binding to ligands or receptors to disrupt vital cancer cell processes and carrying lethal payloads (like radioisotopes or toxins) to the target cell. For instance, Gemtuzumab, a CD-33-specific monoclonal antibody, conjugates with calicheamicin and is used in AML treatment. Ibritumomab tiuxetan, an anti-CD20 antibody, utilizes a 90Y metal isotope in clinical therapy. Monoclonal antibodies also serve in delivering active therapeutics, prodrug activation enzymes, and chemotherapy toxins [11,19,20].

2.4. Vascular targeted agent

Certain proteins are primarily found or more abundant in tumor vasculature, enabling the utilization of various targeting agents like peptides, antibodies, antibody fragments, and nanocarrier systems to specifically deliver photosensitizers (PS) to the tumor vasculature for molecularly targeted photodynamic therapy (molVTP) [21]. Some of these targets exist not just on tumor-associated vasculature but also on cancer cells, facilitating tumor-cell targeted photodynamic therapy (molPDT) [22,23]. Although advancements in molecularly targeting tumor cells have progressed significantly, these studies lie beyond the scope of this review. It's important to note that when both tumor cells and tumor vasculature are targeted, discerning their corresponding effects can be challenging in preclinical studies [24].

2.5. Microtubules destabilizing target agent

MTAs (Microtubule-targeting agents) are a variety of compounds that bind to tubulin, thereby disrupting the dynamic behavior of microtubules (MTs) by either stabilizing or destabilizing the MT polymer. They are categorized into two groups: MT-stabilizing agents (MSAs) and MT-destabilizing agents (MDAs), all binding to specific sites on tubulin dimers [25,26,27]. These agents can eliminate cells during interphase by interfering with processes like vesicular transport, cell morphology, migration, and cell signaling pathways [28]. In cancer treatment, combining MTAs with DNA-damaging agents or in tandem with DNA damage induced by radiotherapy proves highly effective. This efficacy is partly attributed to MTs being crucial for transporting DNA repair proteins to the nucleus, a process disrupted and blocked by MTAs [29].

2.6. Properties of Targeted Drug Delivery [30]

- Biocompatibility: The system should be safe, stable, and compatible within living organisms, both in vitro and in vivo.
- Precise Targeting: Ensuring delivery specifically to target cells, tissues, or organs, ideally achieving uniform distribution and predictable, controllable release rates.
- Independent Drug Release: Drug release mechanisms should not affect the overall delivery process.
- Effective Drug Dosage: Releasing a therapeutic amount of the drug to achieve the intended treatment.
- Minimized Leakage: Preventing drug leakage during transportation to maintain efficacy.
- Biodegradability: Using carriers that can degrade naturally or be eliminated from the body without causing complications or altering the disease state

2.7. Advantages of targeted drug delivery system [31,32]

- Simplified Drug Administration: Targeted delivery often streamlines the drug administration process.
- Reduced Toxicity: By precisely targeting a particular site, the drug's toxicity to other areas is minimized.
- Enhanced Drug Efficacy: Achieving the desired drug response with smaller doses due to focused delivery.
- Bypassing First-Pass Effect: Targeting can bypass the initial metabolism that occurs in the liver, avoiding this process.
- Improved Absorption: Enhancing drug absorption at the intended target site for better effectiveness.
- Steadier Plasma Concentrations: Avoiding fluctuations in plasma concentration levels (no peak and valley effects), providing more consistent and sustained drug action.

2.8. Disadvantages of targeted drug delivery system [33,34]

- Specialized Manufacturing, Storage, Administration: These systems often demand specialized skills and procedures for manufacturing, storage, and administration.
- Diffusion and Redistribution: Controlling drug release, ensuring it reaches the intended site without unintended diffusion or redistribution, can be challenging.
- Fast Clearance: Some targeted systems may be rapidly cleared from the body, impacting their effectiveness.
- Dosage Form Stability: Maintaining the stability of the dosage form throughout the delivery process can be difficult.
- Sophisticated Formulation Technology: Often requiring advanced and complex technology for formulation.
- Cost: The development, production, and implementation of targeted systems can be expensive.
- Lower Yield: These systems might yield comparatively smaller quantities, impacting their availability or cost-effectiveness.

2.9. Challenges for Targeted drug delivery system [35]

These are specific challenges encountered in drug delivery for different types of cancers:

- Eye Cancer (Retinoblastoma): Challenge includes accessing the posterior segment of the eye and prolonging the intra-vitreal half-life of drugs.
- Brain Cancer: Challenges involve achieving uniform drug distribution and enhancing drug diffusion in the brain, which is hindered by the blood-brain barrier.
- Lung Cancer: The challenge lies in ensuring the compatibility of drug particles with the pulmonary system.
- Bladder Cancer: Overcoming the hurdle of drug penetration for deeply embedded tumors within the bladder.
- Peritoneum/Ovarian Cancer: The challenge here is sustaining drug release to prevent nonspecific toxic effects while maintaining an effective therapeutic dose within the peritoneum.
- Skin Cancer (Melanoma): The challenge is to minimize systemic absorption of drugs through the skin while effectively targeting and treating melanoma cells.

Future direction: Future studies and developments of tailored drug delivery systems could go in a number of areas that could greatly enhance the effectiveness of cancer treatment. One of these is creating more accurate targeting techniques for the targeted medicine delivery that is now in use. systems capacity to accurately target cancer cells has been restricted. Additional investigation is required to pinpoint precise targets and create more effective targeting plans.[36]

Diversification of targeted molecules: To produce more precise targeted effects, future research will look for additional molecules, such as more particular aptamers, peptides, and antibodies, that have a specific interaction to tumour cells. New and creative delivery vehicle designs that offer enhanced stability, effective medication loading capacity, and tailored release characteristics will keep being developed and refined. In order to achieve more accurate distribution and greater therapeutic efficacy, the development of multimodal delivery systems, targeted DDS, will not be restricted to a single delivery mechanism but rather will incorporate various delivery tactics.[37]

The use of cancer theragnostics, which combines anticancer targeted therapy with diagnosis by multifunctional nanocarriers containing therapeutic and imaging agents, may prove to be a promising cancer treatment in the future because it enables the selective detection of cancerous cells, their killing with few side effects, their visualisation through real-time in vivo imaging techniques, and real-time monitoring of the treatment's effects. [38]

3. Targeted drug delivery for different diseases-

3.1. Targeted Delivery for Renal Tubulointerstitial Diseases

Proximal tubule-targeted therapies, such as immunosuppressants, steroids, and renin-angiotensin-aldosterone system inhibitors, may be effective medications to stop tubulointerstitial fibrosis and stop the development of chronic kidney disorders. [39]

- **Targeted drug delivery for treatment of osteoarthritis:** Osteoarthritis is associated with severe joint pain, inflammation, and cartilage degeneration. Drugs injected directly into intra-articular joint space clear out rapidly providing only short-term benefit. Drug delivery systems (DDS) that are especially designed to target intra-joint components in the synovium, synovial fluid, and cartilage insets can be developed to extend drug residency and offer long-term osteoarthritis therapy. [40]
- **Veterinary Applications of Targeted Drug Delivery Systems:** The benefits of targeted nanomedicine strategies are slowly gaining recognition as evident from a number of reported studies. Because of the difficulties presented by zoonotic illnesses, targeted drug delivery for the treatment of veterinary infections takes tremendous relevance, not only for enhanced animal health. Every year, over two million people die from over 13 zoonotic illnesses, which include brucellosis, TB, trypanosomiasis, and cysticercosis, among others. These diseases cause 2.4 billion human infections. Both domestic animals and wild animals can contract these illnesses. Global worry is raised by the near contact of people, particularly with such domestic animals. In addition to taking lives, the WHO's "Cull and Kill" program causes significant financial losses for farmers. Nano medication delivery devices combined with targeted treatment approaches may offer a ground-breaking approach that benefits both humans and animals. [41]

3.2. Targeted drug delivery in cardiovascular disease

Cardiovascular disease is the major health issue worldwide and continues to be the primary cause of morbidity and death. Although recent progress in cardiovascular disease management, pharmacological interventions continue to be ineffective due to inadequate pharmacokinetics and increased toxicity [42]. Targeted drug delivery has emerged as a promising method for directing drugs to the specific diseased region. The benefits are dual. Initially, the high efficacy necessitates lower drug concentrations. Second, there will be less detrimental toxic side effects since less medication will reach the healthy parts of the body. Promising targets for targeted drug delivery in cardiovascular disease include endothelial cell inflammation and smooth muscle cell proliferation [43]. Nanoparticle-based medication delivery systems have provided several substantial therapeutic benefits in the treatment of cardiovascular diseases. Nanoparticle-based drug delivery systems modify the biodistribution of therapeutic substances via site-specific, targeted administration and regulated release of precise medications. Metallic, lipidic, and polymeric nanoparticles constitute optimal materials for use in cardiovascular therapies.

Nanotechnology applications in the advantages of reducing cardiotoxicity [44]:

- Optimized delivery strategies reduce distribution in the heart!
- Stimulus-responsive nano-drug delivery systems rapidly iterate.
- Liposomes cannot easily penetrate the endothelial barrier of the heart.
- Targeting the plaque.
- **Targeted drug delivery system to treat asthma-** Asthma is a chronic condition that affects the lungs significantly. Asthma induces inflammation in the lungs and constriction of the airways, leading to wheezing. Patients with asthma suffer from chest tightness, coughing, wheezing, and shortness of breath, all of which lower their quality of life [45]. The airway epithelium is known as an essential controller of the host response to environmental obstacles, including allergens, viruses, and pollutants that contribute to asthma pathogenesis, and is also susceptible to treatment with inhaled nanoparticle-based therapies [46]. New methods of treating asthma, include gene treatments to address the underlying causes of the condition, mucolytic therapy to target airway mucus hypersecretion, and inhalation for the administration of monoclonal antibodies. Monoclonal antibodies (mAbs) offer enhanced specificity relative to these medicines, and mAb treatments are often delivered systemically as a parenteral formulation. Therefore, inhaled administration of targeted medicines may assist decrease off-target effects, improve drug absorption in the airways, and lower dose needs [47].

4. Conclusion

Targeted drug delivery systems offer a promising approach for treating various diseases, including cancer and other conditions, providing improved efficacy and reduced systemic side effects. Researchers should continue to develop more accurate targeting techniques and identify new molecules for targeted delivery. Additionally, the use of cancer theragnostics, which combines anticancer targeted therapy with diagnosis, may prove to be a promising cancer treatment in the future. Targeted drug delivery systems may also be applied to treat other diseases, such as renal tubulointerstitial diseases, osteoarthritis, veterinary infections, cardiovascular disease, and asthma.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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