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BIO-INSPIRED AND BIOMIMETIC DRUG DELIVERY SYSTEMS: A NOVEL APPROACH TO CANCER THERAPY

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ABSTRACT

Cancer continues to be a primary cause of death globally as existing treatments are frequently controlled by non-targeted drug delivery, systemic side effects, quick elimination and resistance to multiple drugs. To reduce these issues, bio-inspired and biomimetic drug delivery systems have arisen as novel strategies to improve therapeutic accuracy and effectiveness. Bio-inspired systems are originating from natural sources including bacteria, viruses, mammalian cells and exosomes to utilize intrinsic biological functions such as immune evasion, tumor targeting and extended circulation. Biomimetic systems are designed to follow these functions, react to stimuli in the tumor microenvironment such as pH, hypoxia, enzymes, and redox potential to facilitate controlled and localized drug release. Hybrid nanocarriers combining synthetic and biological components enhance targeting, stability and biocompatibility even more. Although these advanced platforms show considerable potential in preclinical and initial clinical studies, additional research is required to reduce scalability, standardization, and regulatory issues. In general, bio-inspired and biomimetic drug delivery systems signify a significant change in personalized cancer treatment, providing safer and more efficient therapeutic options.

KEYWORDS: Bio-inspired medication transport, Biomimetic nanoscale carriers, Precision medication delivery, Bacteria-assisted therapy, Hybrid medication delivery systems, Regulated drug release.

1. INTRODUCTION

Cancer ranks among the most widespread and life threatening illnesses globally, resulting in millions of fatalities annually. Despite ongoing progress in chemotherapy, radiotherapy and immunotherapy, the efficacy of traditional treatment methods still faces significant limitations. Key obstacles include the non-specific delivery of medications, swift systemic clearance, low solubility and considerable toxicity to healthy tissues. Furthermore, factors such as multi-drug resistance and the intricate nature of the tumor microenvironment further diminish therapeutic effectiveness. These challenges highlight the pressing requirement for innovative and more effective drug delivery methods in cancer treatment.[2,3,12]

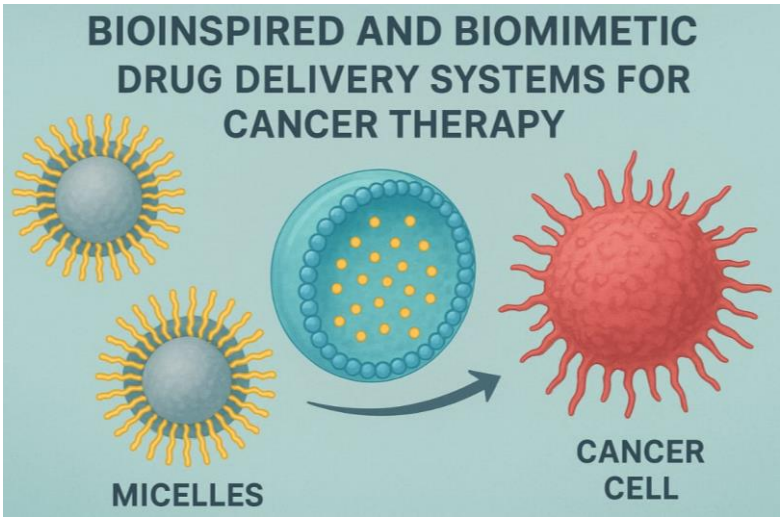

Figure 1: Bioinspired and Biomimetic Drug Delivery Systems for Cancer Therapy.

Recently, bio-inspired and biomimetic drug delivery systems have surfaced as promising alternatives to standard nanocarriers. These systems leverage principles from nature to improve therapeutic efficacy and safety.[3,15] Bio-inspired systems are directly derived from natural origins such as cell membranes, exosomes, viruses, peptides and proteins, inheriting beneficial properties like immune evasion, extended circulation and innate targeting capabilities.[5] In contrast, biomimetic systems are artificially crafted to replicate such biological characteristics, often designed to mimic natural processes such as cell-cell communication, targeting tumors and responding to stimuli like pH levels, enzymes and redox conditions.[6,8]

The use of bio-inspired and biomimetic approaches in oncology presents several benefits. These advantages include targeted delivery to tumor locations, diminished off-target toxicity, enhanced drug stability and the potential to address multidrug resistance. By merging biological functions with cutting edge nanotechnology, these delivery mechanisms set the stage for more effective, safer and individualized cancer treatments.[15,17]

2. BIO-INSPIRED DRUG DELIVERY SYSTEMS FOR CANCER THERAPY

2.1. BACTERIA INSPIRED DRUG DELIVERY SYSTEM

The application of bacteria in cancer therapy dates back nearly a century to William Coley. He witnessed tumors decrease in size in a patient with erysipelas. His research laid the groundwork for contemporary bacterial treatment. Bacteria possess distinct characteristics, including the capability to flourish in regions with low oxygen and in dying tumors. They can additionally emit detectable signals, making them appropriate for targeted cancer treatment. Species such as Bacillus, Bifidobacterium, Listeria, Salmonella, Mycobacterium and Clostridium demonstrate anticancer properties. By means of genetic engineering, bacteria can be altered to transport drugs, proteins, enzymes and genes, with various methods currently undergoing clinical trials. One method employs the Synchronized Lysis Circuit (SLC), which regulates bacterial proliferation and medication release. When exposed to 5-Fluorouracil (5-FU), SLC-3 bacteria successfully inhabited tumors and diminished systemic inflammation.[13,16]

2.1.1. Bacterial Phantoms (BPs)

BGs are inert structures formed by Gram-negative bacteria. They are created by expressing the E lysis gene from bacteriophages. In a study, Mannheimia haemolytica ghosts effectively transported doxorubicin (DOX) to colorectal cancer cells, enhancing the cytotoxicity twofold compared to free DOX. BGs reduce side effects because they do not colonize and preserve surface structures to influence the immune response.[13]

2.1.2. Micro-robots

Microbots consist of living bacteria connected to nanoparticles that carry drugs. This arrangement removes the requirement for genetic alteration. These systems exploit the invasiveness of bacteria to focus on tumor regions with low oxygen levels. For instance, Listeria monocytogenes linked to nanoparticles via biotin–streptavidin interactions introduced plasmid DNA into cells, leading to protein expression. In a different instance, S. Typhimurium-directed paclitaxel-loaded liposomes exhibited quicker mobility and a more

potent tumor-eradicating effect compared to each component separately. Biohybrid systems combine bacterial cells with synthetic microbots, enhancing functionality and reducing mutation risks.[3]

2.2. VIRUS INSPIRED DRUG DELIVERY SYSTEM

Viruses are tiny infectious agents made up of nucleic acids and a protein coat. Recently, they have been employed as gene delivery vectors in cancer therapy due to their ability to convey genetic material into host cells. Employing viral vectors with medications enhances anticancer efficacy through the integration of gene transfer and drug delivery. Frequently used viruses consist of adenoviruses, adeno-associated viruses and retroviruses. Research showed that nanoparticles connected to adenovirus capsid proteins could detect tumor cells while maintaining infectivity. Moreover, gold nanoparticles (for hyperthermia) were integrated with adenoviral vectors targeting carcinoembryonic antigens, maintaining tumor specificity and viral functionality. These methods demonstrate the potential for merging nanotechnology with virotherapy to create multifunctional cancer treatments.[13]

2.2.1. Virus-Like Particles (VLPs)

VLPs are non-infectious viral shells that are self-assembled and lack genetic material. They can infiltrate cells and deliver therapeutic agents like drugs, peptides and antigens. They are dependable, easy to manage, cost-effective and suitable for nanomaterial production. Paclitaxel-loaded MS2 VLPs preserved capsid functionality. Another research showed that MS2 VLPs preferentially delivered DOX, cisplatin and 5-FU to hepatocellular carcinoma (HCC) cells with a tenfold higher affinity than to non-cancerous cells. As a result, VLPs enable focused delivery to particular cells and effectively remove cancer cells in vitro.[13,16]

2.2.2. Virosomes

Virosomes are viral particles that have been reconstructed, comprising influenza glycoproteins (hemagglutinin and neuraminidase) and feature an empty interior. They promote receptor-mediated endocytosis and escape from endosomes, protecting therapeutic agents from degradation. A magneto-haemagglutinin virosome delivered decitabine to prostate tumors more effectively than the free drug, using lower doses.[13]

2.2.3. Particles That Imitate Viruses

Virus-inspired designs provide improved drug retention and targeting. Influenced by the thread-like form of viruses, filomicelles (derived from self-assembling amphiphilic block

copolymers) can avoid immune removal and persist in circulation for an extended duration. Research indicates that paclitaxel-loaded filomicelles decreased tumor size more efficiently than paclitaxel in solution form. Moreover, pH-responsive virus-like nanogels containing tumor-targeting ligands and DOX-filled hydrophobic cores were created to imitate viral capsid structures. These systems integrate virus-like characteristics and capabilities to enhance targeted drug delivery.[16]

2.3. DRUG DELIVERY MECHANISMS DRIVEN BY MAMMALIAN CELLS

Mammalian cells offer promising platforms for drug delivery due to their biocompatibility, natural targeting abilities, and interaction with the body. Novel nanosystems featuring unique functions have been developed by merging synthetic nanoparticles (NPs) with different cell types, such as erythrocytes (RBCs), immune cells, stem cells and platelets.[13,16]

2.3.1. Erythrocytes (RBCs)

RBCs are abundant, versatile and eco-friendly, with prolonged circulation times (120 days in humans). They can encapsulate drugs and provide large surface areas for alteration while preserving biological activity. Techniques for drug incorporation include electroporation, endocytosis and hypo-osmotic swelling. RBC membrane-coated nanoparticles (RBCm-NPs) exhibited controlled release of DOX and extended circulation, proving effective in treating blood cancers. Micromotors derived from RBCs, loaded with DOX, CdTe quantum dots and magnetic nanoparticles, enabled simultaneous drug delivery and imaging, demonstrating theranostic potential. Nevertheless, the immune system may swiftly eliminate RBCs after modification and factors associated with processing (blood source, preparation method) can affect drug stability.[13]

2.3.2. Immune Cells

Immune cells, especially white blood cells (WBCs) can cross physiological barriers and migrate to areas of inflammation or tumors, making them ideal for targeted therapy. Macrophages are able to consume detrimental cells and migrate towards tumors. When combined with drug-encapsulated nanoparticles (e.g., DOX liposomes), they act as Trojan horses, effectively penetrating tumors (e.g., gliomas) and preserving drug efficacy. Neutrophils, abundant in the blood, can infiltrate brain tumors. They have been used to deliver paclitaxel or albumin nanoparticles post-surgery, improving survival by targeting inflamed tumor regions.[16]

2.3.3. Stem Cells

Mesenchymal stem cells (MSCs) possess a robust ability to target tumors and are beneficial for delivering genes and drugs. MSCs containing PLGA-DOX or silica nanorattles successfully targeted lung metastases and brain tumors while maintaining their functionality. Their capacity to move and hold onto medications in tumor locations is undergoing additional research for better comprehension and utilization.[13]

2.3.4. Thrombocytes

Platelets play a role in blood coagulation and are naturally attracted to circulating tumor cells (CTCs). Their lifespan of approximately 8 to 9 days enables extended distribution of therapeutics. Platelets attached to anti-PDL1 antibodies delivered the therapy upon activation, decreasing tumor recurrence after surgery in models. Nanovehicles coated with platelet membranes (PM-NV) sequentially delivered TRAIL and DOX, triggering apoptosis pathways and destroying metastatic cells, demonstrating combined antitumor effects.[13]

2.4. CELL INSPIRED DRUG DELIVERY SYSTEMS

Cell-inspired systems replicate biological processes to improve drug delivery, particularly emphasizing exosomes and cancer cell membranes for their inherent targeting and immune-evasive characteristics.[3]

2.4.1. Exosomes

Exosomes are tiny, amphiphilic vesicles that are naturally released by cells and present in fluids such as blood and urine. Made up of a hydrophilic core and lipid bilayer, they are environmentally friendly, compatible with biological systems and show minimal immune response. Their membrane can merge with target cells, improving drug uptake, while their tiny size facilitates tumor infiltration and avoidance of phagocytosis. In a study, exosomes derived from immature dendritic cells (imDC) were modified with iRGD peptide to target tumors and were filled with DOX. This iRGD-exosomes demonstrated significant antitumor efficacy both in vitro and in vivo. Exosomes are capable of transporting a range of therapeutic payloads such as drugs, proteins and siRNA/microRNA, shielding them from degradation. Despite showing potential in clinical trials, exosome-based delivery needs further investigation because of the insufficient comprehension of their intricate signaling functions.[13]

2.4.2. Membranes of Cancer Cells

Membranes from cancer cells can serve to cover nanoparticles (NPs) for homotypic target utilizing the inherent inclination of cancer cells to identify and connect with one another. A system utilized ICG/PLGA nanoparticles (ICNPs) that were coated with cancer cell membranes, providing photothermal treatment, dual-modal imaging (FL/PA) and targeting specific to tumors. A different study utilized MDA-MB-435 cancer cell membranes to develop cancer cell nanoparticles (CCNPs). These core shell configurations resembled the antigen characteristics of cancer cells and demonstrated improved adhesion and targeting through homotypic interactions.[13]

2.5. LIPID-DRIVEN MEDICATION TRANSPORT MECHANISMS

Lipid-based drug carriers are commonly utilized because of their biocompatibility, capacity to encapsulate hydrophobic medications and potential for targeted delivery, particularly in cancer treatment.[13]

2.5.1. Solid-Lipid Nanoparticles (SLNs

SLNs consist of solid lipid centers stabilized by surfactants, facilitating hydrophobic drug transport in water-based environments. Their nanostructure (50–1000 nm) enables parenteral and oral administration, utilizing intestinal lymphatic transport. SLNs can penetrate the blood-brain barrier (BBB) through interactions with endothelial cells and plasma proteins. A study found that Cholesterol-PEG-coated SLNs (C-PEG-SLNs) containing DOX exhibited enhanced stability, targeted tumor delivery and effectiveness against multidrug-resistant (MDR) breast cancer cells without notable side effects. Their pH-sensitive properties, prolonged circulation and EPR effect render them a potential solution for addressing MDR and enhancing chemotherapy.[13]

2.5.2. Liposomal structures

Liposomes are vesicles formed from phospholipid bilayers that encapsulate and transport drugs. They can be customized in composition, structure and size to improve stability and targeting. Vesosomes, which are multi-compartment liposomes, enable localized and prolonged drug release via compartmental diffusion. They are simple to produce, able to transport various cargoes and can be adapted with surface coatings for improved stability and specificity. Niosomes, like liposomes but composed of non-ionic surfactants and cholesterol, provide enhanced stability, rigidity and economical advantages. Their adaptability in formulation renders them appropriate for topical, ophthalmic and cancer treatments. For

instance, transferrin-conjugated DOX-loaded niosomes demonstrated targeted cytotoxic effects in different cancer cells. They may also be developed as thermosensitive systems, broadening their use in regulated drug delivery.[16]

3. BIOMIMETIC SYSTEMS FOR DRUG DELIVERY IN CANCER THERAPY

Traditional nanocarriers effectively enhance drug solubility and stability but often fail to target tumors accurately due to rapid clearance, low cellular uptake and non-specific biodistribution. To address these limitations, biomimetic drug delivery systems have emerged as a powerful strategy for cancer treatment. Unlike bio-inspired systems that are directly derived from nature, biomimetic systems are artificially created platforms designed to emulate natural biological structures and functions, thereby combining the advantages of both biology and nanotechnology.[2,4,6]

3.1. TUMOR MICROENVIRONMENT–RESPONSIVE SYSTEMS

Tumor tissues exhibit a distinct tumor microenvironment (TME) characterized by an acidic pH, hypoxia, overexpressed enzymes and heightened redox potential. Biomimetic nanocarriers can be engineered to respond to these stimuli, facilitating controlled drug release specifically at the tumor site. The pH-sensitive nanocarriers are designed to release drugs in the acidic environment of tumor tissue while remaining stable in healthy tissues. Enzyme-sensitive carriers leverage the overabundance of proteases (such as MMPs) present in tumors to trigger drug release. Hypoxia-responsive systems activate under low oxygen conditions, enhancing selectivity.[2,8,10]

3.2. SYNTHETIC VESICLES IMITATING BIOLOGICAL MEMBRANES

Polymersomes, micelles and liposomes can be tailored to replicate natural cell membranes, leading to improved biocompatibility and circulation duration. Enhancements in tumor specificity can be achieved through the functionalization of targeting ligands (such as antibodies, peptides and aptamers). Recent innovations also involve hybrid vesicles that resemble exosomes, providing effective drug delivery and fostering intercellular communication.[4]

3.3. NANOPARTICLES IMITATING IMMUNE CELLS

Cancer cells possess mechanisms for evading the immune system, making immune-based biomimicry a particularly promising strategy. Nanocarriers designed to mimic macrophages, neutrophils, or natural killer (NK) cells can selectively target tumor tissues and areas of

inflammation. Immune-mimetic nanoparticles not only enhance targeting efficiency but also influence the immune microenvironment of the tumor, creating opportunities for combined immunotherapy with chemotherapy or checkpoint inhibitors.[6,10]

3.4. ARTIFICIAL EXOSOME-LIKE NANOCARRIERS

While natural exosomes offer significant potential as drug delivery vehicles, challenges remain in their large-scale isolation and production. To address these challenges, researchers have developed synthetic exosome-mimetic vesicles. These carriers emulate the size, structure and functional proteins of native exosomes whereas allowing for large scale production. They feature improved stability, tumor tissue penetration and the ability to deliver nucleic acids (such as siRNA, miRNA and CRISPR reagents) for gene therapy.[2,4]

3.5. HYBRID BIOMIMETIC NANOCARRIERS

Recent advancements combine synthetic nanoparticles with biological shells (like a polymer core encased in a cell membrane or peptide shell). These hybrid systems merge the stability and adaptability of synthetic nanocarriers with the biological functionality of natural materials. These platforms offer prolonged circulation, active targeting, immune evasion and stimuli-responsive drug release making them highly promising for personalized cancer therapy.[11]

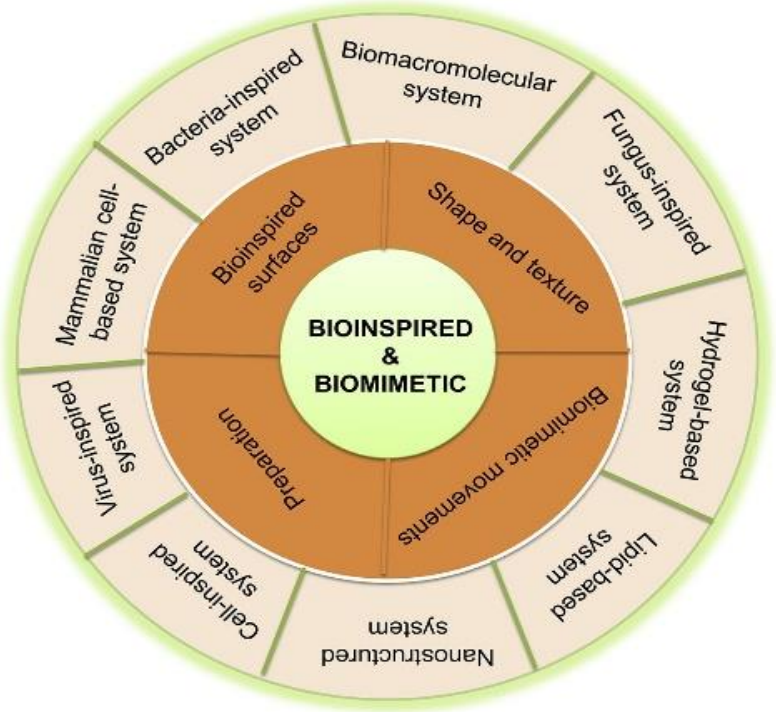

Figure 2: Different types of bioinspired and biomimetic drug delivery system.

4. RESULTS AND DISCUSSION

Bio-inspired and biomimetic drug delivery systems have demonstrated significant potential in addressing the main challenges of traditional cancer therapies including non-specific distribution, quick systemic clearance and multidrug resistance. Bio-inspired systems encompassing those based on bacteria, viruses, mammalian cells and exosomes, utilize inherent biological traits like tumor targeting, immune evasion and extended circulation. For example, bacterial systems such as SLC-modified strains and bacterial ghosts have facilitated targeted drug delivery to tumors. Virus-derived systems like VLPs and virosomes improve the delivery of targeted genes and drugs. Likewise carriers based on mammalian cells such as erythrocytes, immune cells, stem cells and platelets provide inherent targeting and biocompatibility. Exosomes and nanoparticles coated with cancer cell membranes enhance cellular uptake and tumor-targeting capabilities because of their inherent biological surface markers.

Lipid-based systems such as solid-lipid nanoparticles, liposomes and niosomes continue to be essential for encapsulating hydrophobic drugs while facilitating controlled, targeted release. Biomimetic systems have been created to emulate biological actions, allowing them to react to characteristics of the tumor microenvironment like pH, enzymes and low oxygen levels, which facilitates targeted drug delivery. Nanoparticles that mimic immune cells and artificial exosome-like nanocarriers improve tumor targeting and drug stability. Hybrid systems that merge synthetic cores with biological membranes provide a robust blend of stability, targeting and immune evasion. Although these innovative platforms have shown promising results in preclinical studies, issues like large-scale production, reproducibility and clinical translation need to be resolved for effective use in personalized cancer treatment.

5. CONCLUSION

The development of bio-inspired and biomimetic drug delivery systems marks a major breakthrough in cancer treatment. By utilizing natural biological processes or mimicking them by engineered platforms, these systems provide better targeting, diminished systemic toxicity, increased drug stability and the capacity to address multidrug resistance. Ranging from bacterial and viral vectors to carriers derived from mammalian cells and lipid-based nanoparticles, every method uniquely helps in overcoming the shortcomings of traditional therapies. In spite of encouraging outcomes in early clinical and preclinical trials, obstacles persist in scaling up production, ensuring standardization and obtaining regulatory approval.

Ongoing interdisciplinary research and development are crucial for transforming these innovative systems into clinically feasible solutions. Through additional refinement, bio-inspired and biomimetic delivery systems possess significant potential to transform cancer therapy and facilitate more efficient, tailored treatment strategies.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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