



TARGETED DRUG DELIVERY SYSTEM FOR THE TREATMENT OF CANCER THERAPY

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Abstract

The characteristics of the cancer that offer chances for medication delivery systems to target cancer this term are highlighted in this article. The most promising approach that can bypass has received a lot of attention despite the fact that chemotherapy-based targeted medication delivery has been the subject of much research. The extensive introduction of targeted delivery techniques based on different nanocarriers to incorporate small molecule chemotherapies in the treatment of cancer was also addressed in this review. The difficulties in using a tailored medication delivery system to treat cancer are also mentioned in this article.

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1. Introduction

One of the leading causes of death worldwide is cancer. [1] Every year, more than eight million individuals worldwide pass away from cancer. [2] Multiple, subsequent gene alterations that affect how cells function are the root cause of cancer.[3] Genetic alterations can cause abnormalities in the structure of cells, such as cancer. [4] Chemotherapy, surgery, and radiation therapy are three main cancer treatments. [5] The utilisation of drug delivery systems is one of the most popular ways to guarantee the targeted absorption of therapeutic drugs in the body. Different drug carriers comprised of polymers, dendrimers, cell-derived membranes, exosomes, and surfactants have been created to improve the therapeutic effectiveness of pharmaceuticals.[6] In strategies for treating recurring cancer, chemotherapy and radiation therapy are usually combined. [2] Each of the many millions of tiny cells that make up our body is a unique living organism. Your body's cells generally cooperate with one another to produce tissues and organs. An illustration of how this collaboration occurs is in the capacity for self-replication of your cells. The body's regular cells initially divide and grow properly before stopping. Once that happens, they only start to multiply when it's time to replace any damaged or dead cells. Cancer arises when this cellular reproduction mechanism spins out of

control. [7] In other words, cancer is a condition marked by haphazard, unwanted, and unplanned cell division. Contrary to healthy cells, cancer cells continue to grow and divide during their entire lifespan, giving rise to a growing number of potentially harmful cells [8].The DNA (genetic material inside cells that determines biological features and functioning) of cancer cells has been damaged, which accounts for the aberrant growth and division seen in these cells. Cellular DNA may be damaged and flawed in a number of different ways. For instance, environmental influences (such as smoking) can set off a series of occurrences that culminate in cellular DNA abnormalities that cause cancer. Alternately, you can get faulty DNA from your parents. [9]Tumors are collections of cancer cells that frequently arise as cancer cells multiply and divide. By compressing, crushing, and obliterating the non-cancerous cells and tissues around them, tumors are responsible for many of the symptoms of cancer.[10]Tumors come in two varieties: benign and malignant. Benign tumors do not grow and spread as widely as cancerous ones since they are not malignant. Typically, benign tumors do not pose a threat to life. Malignant tumours, on the other hand, enlarge and spread throughout the body. Cancer cells spread by the process of metastasis from the primary tumour site to different parts of the body. [11]

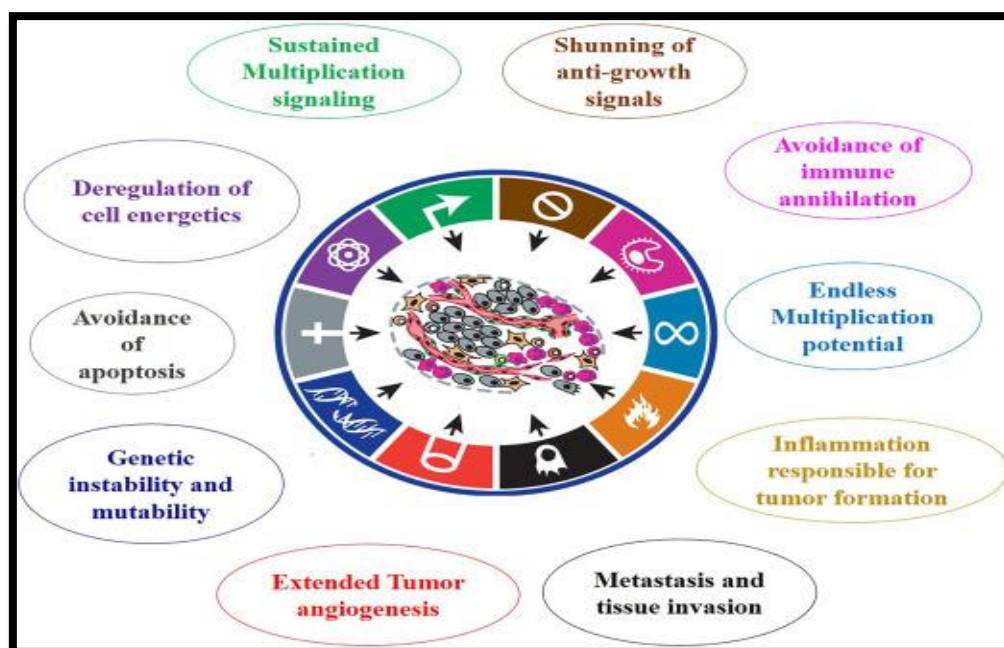


Fig.1 Various risk factors induce the cancer cell in body system [12]

Criteria for Major Depressive Disorder (MDD)[13]

A diagnosis of Major Depressive Disorder (MDD) is made when a person exhibits five or more of the symptoms listed below almost daily over a period of two weeks, with at least one of the symptoms being a depression or a decline in enjoyment or interest.

1. Oversleeping or difficulty getting asleep.
2. Weakness and exhaustion
3. A sudden shift in appetite that causes a 5% shift in weight (gain or loss) within a month.
4. guilt, shame, and a sense of worthlessness
5. the inability to concentrate, think clearly, or make decisions.
6. Anger, irritability, and restlessness
7. Passivity and a lack of participation in routinely pleasurable activities
8. a feeling of hopelessness and despondency
9. having suicidal or fatal thoughts.

Targeting delivery strategy [14,15,1]

Chemotherapeutic drugs have a variety of disadvantages, including the development of

resistance, disruption of the metabolic activities of healthy cells, and nonspecific targeting. The main cancer immunotherapies that come under these categories are monoclonal antibodies, oncolytic viruses, cancer vaccines, and adoptive T cell transfer. The bone marrow microenvironment is crucial for preserving cell renewal and differentiation, especially for cancer cells. The bone marrow has a large number of blood vessels and capillaries. Numerous types of cells, including osteoblasts, osteocytes, fibroblasts, mesenchymal stem cells, macrophages, and osteoclasts, make up this system. Which is recognized as one of the most complex. By boosting the concentration of the drug in specific areas of the body relative to others, targeted drug delivery has been used to increase the efficacy and reduce the toxicity of the treatment. One of these ideal targeting ligands for the targeted administration of medicinal and imaging drugs to inflammatory and cancerous tissues is FA.

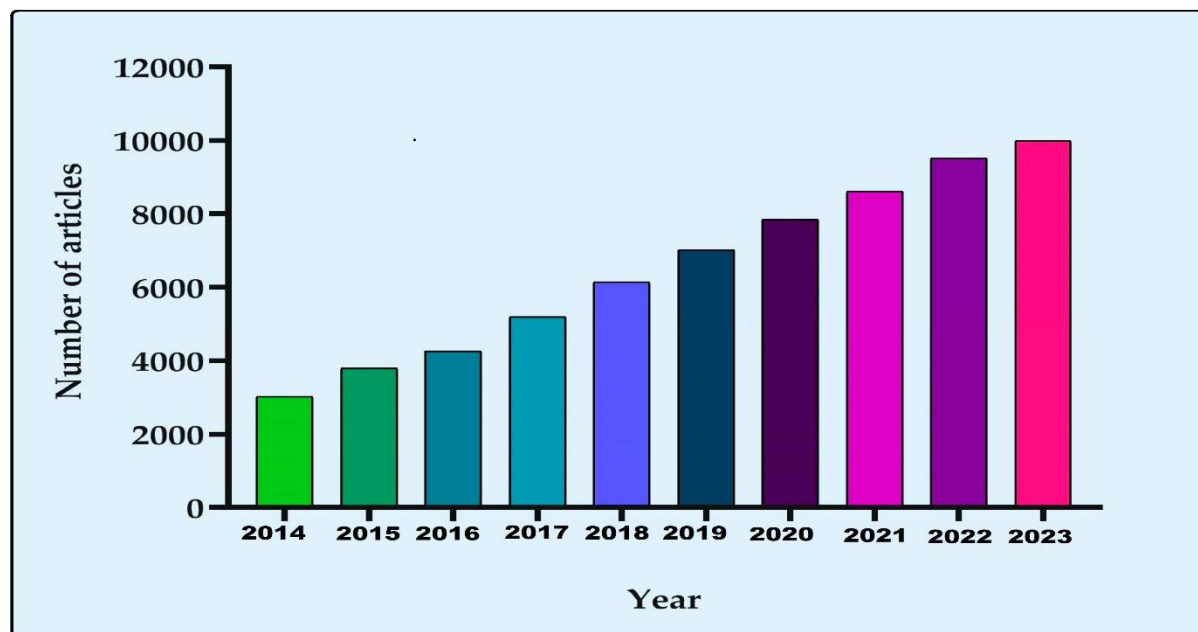


Fig.2. Growth in the number of published articles Since the focus of this paper is on target-based drug delivery for cancer therapy [16]

Passive Targeting Strategy: Passive targeting relies on the drug delivery system growing at a certain end organ or tumor location. It makes use of leaky vasculatures, which in essence require a delivery system for their own characteristics, including size, shape, surface zeta potential, and other traits. The number of

reticuloendothelial cells in the bone marrow vasculature is related to the degree of drug buildup in the bone.

Active Targeting Techniques: Active targeting improves delivery that concentrates on tumor tissues. Peptides, antibodies, and

tails may be attached to the surface of nanomedicines in order to deliver medications. Numerous cancer cells have distinct surface indicators that are targetable. The common

strategy of targeting peptide-modified nanomedicines has been extensively investigated in drug delivery research.

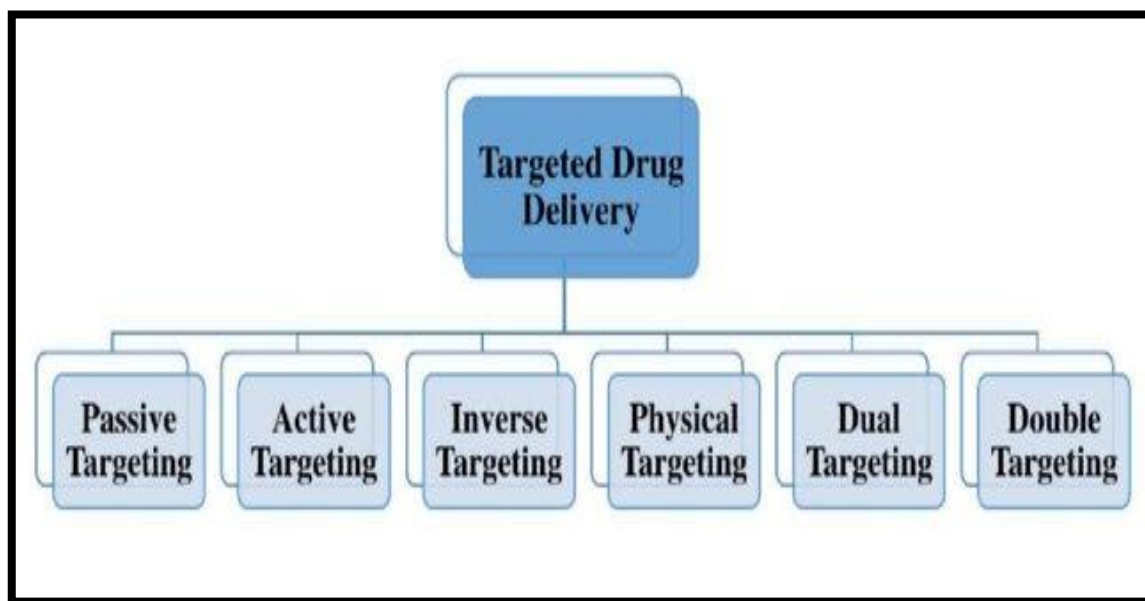


Fig.2 Targeted Drug Delivery Carriers Used in Nanobiomedical Applications [17]

Types of cancer [18]

One of the top five most deadly tumors, liver cancer is the only one whose incidence is rising each year. The hepatitis B and C viruses, smoking, diabetes, obesity, and other dietary exposures can all result in liver cancer. The prognosis for people with liver cancer is not good.

Lung cancer:

Lung cancer is the leading cause of cancer-related deaths in both men and women globally. Lung cancer incidence and mortality are strongly correlated with smoking habits.

Breast Cancer:

The mismatch between proliferation and apoptosis considerably hinders the removal of damaged cells by apoptosis. In tumor-affected cells, triggering apoptotic pathways is a crucial component of cancer treatment.

Colon cancer:

Colon cancer is one of the most common cancer forms globally and one of the main causes of mortality, along with lung, prostate, and breast cancer. Over 65s have a larger chance of having colon cancer than younger adults. In this age bracket, tumor incidence

accounts for 75% of all cases.

Different cancers Multiple myeloma (MM)

Different cancers Multiple myeloma (MM) is an aggressive and incurable B-cell malignancy in people. MM patients frequently exhibit hypercalcemia, immunodeficiency, infection, renal failure, anemia, and renal failure as clinical symptoms. Due to medication resistance and undesirable side effects, pharmacological therapy for MM still faces difficulties. MM continues to be an incurable hematological cancer.

Cancer-treating antibodies' modes of action [19]

A single therapeutic antibody can develop into a variety of different therapeutic agents, such as CAR T cells, radioimmunoconjugates, bispecific antibodies (BsAbs), and antibody-drugconjugates (ADC) In contrast to small-molecule TKIs, antibodies that target growth factor receptors have a different mode of action. In contrast to TKIs, which only target activating mutations in the kinase domain and are therefore effective in a minority of patients, antibodies provide therapeutic benefit to all patients who overexpress the targeted antigen independent of its mutation status.

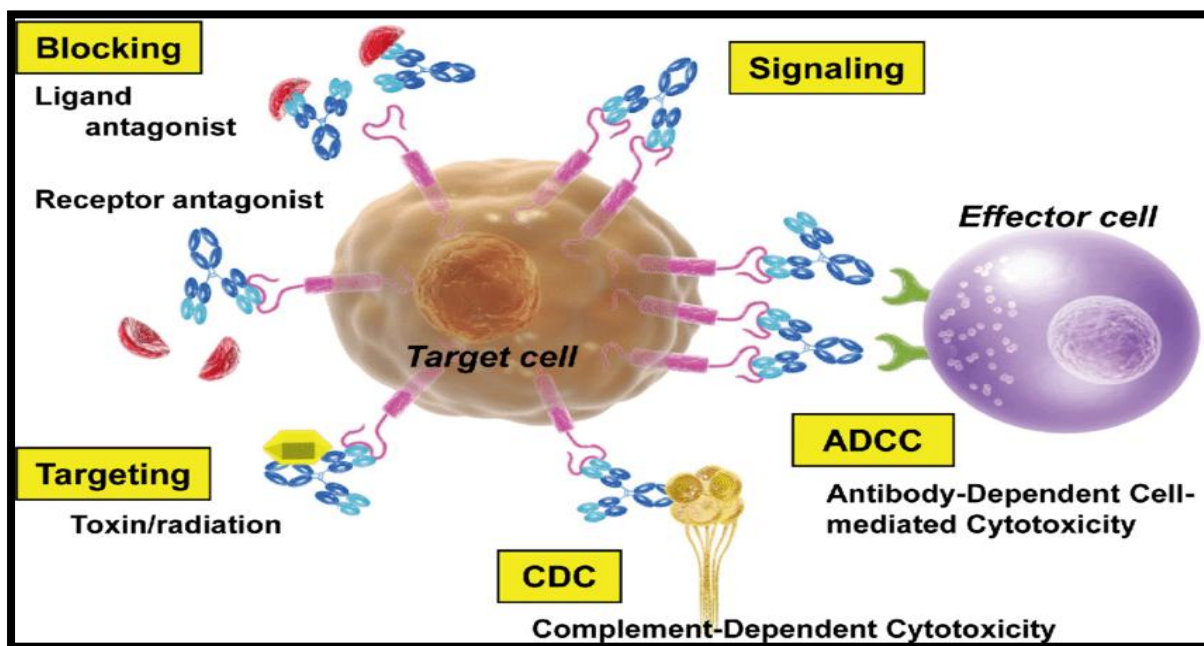


Fig.3: Mechanisms of Action of Therapeutic Antibodies.[20]

I. Targeted "drug delivery" methods for mitochondria [21]

In order to discover how to get anticancer drugs into the mitochondrial matrix of cancer cells in a way that targets the mitochondria, many compounds that target the mitochondria and have different driving forces have been researched. Anticancer drugs, macromolecules

(like polymers) that can be transformed into drug-loadable nanoparticles, and already-formed nanocarriers can all be chemically linked to the moieties. either with or without a brief chemical bridge, Under the control of the mitochondrial-targeting moiety, the Under the control of the mitochondrial-targeting moiety.

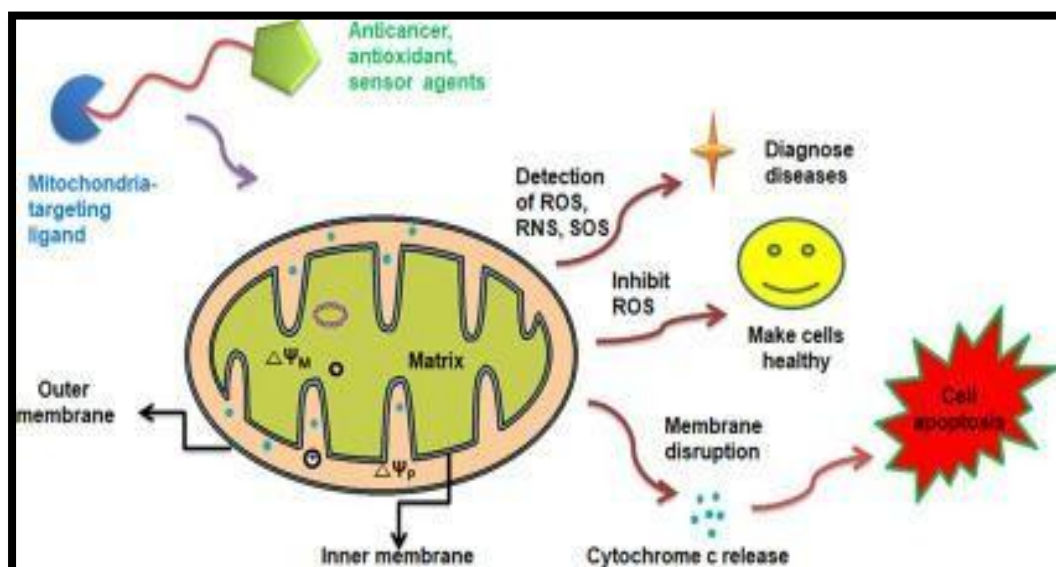


Fig.4 Mitochondria-Targeted „Drug Delivery“ System[22]

II. Delivery mediated by ligand receptors [23]

Many proteins require iron to make the heme groups, which are renowned for their ability to

bind and transport oxygen. Iron is a crucial component of many proteins. This is known as transferrin-based targeted delivery. Deoxyribonucleic acid (DNA) production and

electron transport are two more metabolic activities that require iron. Tf's ability to penetrate the BBB has stimulated extensive study of gliomas and their treatment. The BBB, a highly selective semipermeable border of capillary endothelial cells, is one of the few selective chemical barriers that Tf can overcome. Transferrin receptors are mostly expressed in the body's RBCs (red blood cells), brain endothelial cells, and many malignant cell types. Tf receptors make a good target for targeted therapy because it is known that they are overexpressed on both tumor cells and brain capillary endothelial cells in gliomas.

III. Folic Acid-Based Targeted Delivery

As a B vitamin, folic acid (FA) is easily purchased and ingested. FA is crucial for the synthesis of purines and pyrimidines, which allows it to control cell division and proliferation. Folic acid was attached to the surface of hollow mesoporous structured upconversion luminous nanoparticles (HMUCNPs) via an amide reaction to enhance the targeted delivery of anticancer drugs. Folic acid is a well-known ligand for the selective targeting of pharmaceuticals into tumour cells. An study of the samples' features revealed that they had a typical hollow mesoporous structure and significant upconversion luminescence. They become valuable for cell imaging and medicine administration as a result. Drug storage and release characteristics have been shown to be pH-responsive, suggesting that focused drug release and controlled therapy at diseased locations may be advantageous at the lower pH in some malignant tissues.

IV. Targeted Delivery Using Hyaluronan

The CD44 receptor functions as an adhesion regulator in hematopoiesis and lymphocyte activation by binding to hyaluronan or hyaluronic acid. High levels of CD44 are found in some migratory malignancies, such as lymphomas. Hyaluronic acid (HA), a substantial component of the extracellular matrix, has been employed extensively in the pharmaceutical and cosmetic industries due to its alleged pharmacological properties, which include anti-aging, anti-inflammatory, skin healing, tissue regeneration, and wound recovery capabilities. High moisture retention,

strong biocompatibility, and tuneable viscoelastic properties are all characteristics of HA. Different molecular weights of HA have unique characteristics controlling a range of biological processes, such as cell division, migration, differentiation, vasculogenesis, and angiogenesis, as well as cell adhesion and motility, depending on the molecular weight of the cells, the proper balance between HA synthesis and degradation is essential.

Challenge in drug delivery system for treating cancer [7,16,1]

Numerous articles outline the challenges of treating cancer and suggest remedies. Clinical and Manufacturing Challenges, a feature shared by passive and active targeting. In addition to the prerequisites for a triggered release and a restricted payload spring at the moment of action that were already mentioned, active and passive targeting present issues in manufacturing and medicine.

Commercialized Obstacles

One of the main business barriers to clinical translation is creating a predictable and repeatable synthesis process. It is easier and largely dependent on the operator's skill to work on a small-scale formulation in a lab, but these conditions are unsuited for consistent large-scale production.

Regulatory/Policy Challenges

Another pressing and serious issue that has to be addressed is the large gap between scientific research and regulatory agencies. The majority of governments are responsible for ensuring that new medications are approved in line with a variety of rules and laws, including those controlling safety profiles, ideal methods for industrial manufacturing, intellectual property rights, quality controls, etc.

Targeted drug delivery systems and their limitations [24]

On the other hand, targeted pharmaceutical delivery systems that spare healthy cells specifically target cancer cells. The recent development of liposomes, antibodies, immunoconjugates, immunotoxins, and polymer conjugates is just one example of targeted nanodrug delivery techniques. In this overview, some of these delivery methods are

covered, with a focus on the liposomal drug delivery system. These microstructures can include extremely intractable and/or unstable medications that can be administered in certain ways because the mechanical and physicochemical properties of these delivery systems differ from those of the lipids that make up each of their individual constituents.

Certain qualities, such as the following, must be present in the targeted drug delivery system:

1. It must be biodegradable, stable, harmless (non-toxic), and compatible with bodily fluids.
2. Only deliver the medication to the intended spot.
3. Set a predefined rate for drug release.
4. The pharmacological action is unaffected by the drug's release rate.
5. Minimal drug leakage while being transported to the intended location.
6. Using a carrier that is neutral, biodegradable, or simple to remove.
7. The drug delivery system should be easy, inexpensive, and simple to prepare.

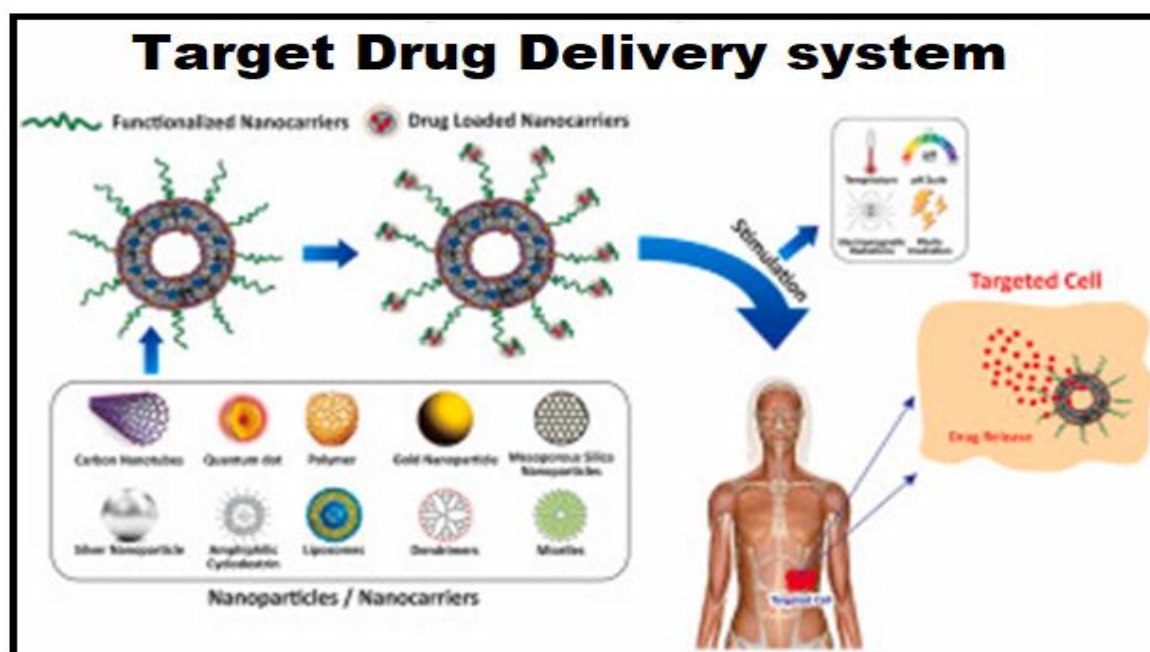


Fig.5 A variety of nanocarriers for medication delivery [25]

Environmental cancer risk factors [26]

Physical factors

Ionizing radiation is one of the most frequently mentioned carcinogens, which can lead to tumors in any organ where cancer develops on its own. The observations of the kids who made it through the bombings of Hiroshima and Nagasaki and children who had received prenatal RTG, the first research on the risks of ionizing radiation was conducted in the middle of the 20th century [27]. Leukemia and thyroid cancer are now more common. Ultraviolet radiation: UV light is the environmental factor that affects the skin the most frequently and most adversely. Chronic and excessive sun exposure typically results in late-stage symptoms of accelerated skin aging and even post-solar carcinogenesis, in addition to early-onset issues like erythema or sunburn.[28,29]

Chemical factors

Smoking tobacco: With an annual mortality toll of about 6 million, tobacco use is the biggest preventable risk factor for cancer death. All tobacco products, whether derived entirely or in part from tobacco leaves used for smoking, chewing, or sniffing, are sources of numerous carcinogens and other harmful substances, according to the WHO FCTC.

Alcohol: According to epidemiological research, drinking alcohol raises your risk of developing cancer. Alcohol consumption raises the chance of developing cancers of the liver, breast, mouth, throat, larynx, and esophagus.[30].

Other chemicals:

There are a number of chemicals used in homes, agriculture, the environment, and the development of civilization in general. An increase in the presence of hazardous substances causes genetic mutations. Industrial pollution, hazardous industrial waste, and vehicle exhaust emissions increase the risk of cancer in children.

Biological factors[31]

Diet: Improper eating habits are one of the main causes of malignant tumor formation. Due to the development of civilization, several toxic substances with cancer-causing actions can be found in food, the environment, and the surroundings.

Food containing mutagenic and carcinogenic substances: Depending on the environment, food contains mutagenic and carcinogenic substances. These may be created naturally or as a result of the preparation and preservation of food. Most of them are genotoxins, which are active mutagens that bind covalently to DNA molecules and change the nitrogen base. This changes the sequence of amino acids in proteins, which are then made from the new sequence.

Infections: Researchers are becoming more and more focused on how infectious microorganisms contribute to the genesis of various diseases, including cancer.

2. Conclusion

Chemotherapy is a common cancer treatment method, but it has disadvantages like resistance development, disrupting healthy cell metabolism, and nonspecific targeting. Monoclonal antibodies, oncolytic viruses, cancer vaccines, and adoptive T cell transfer are examples of primary cancer immunotherapies. By supplying ligands with a high affinity for particular receptors, targeted medication delivery boosts effectiveness and lowers toxicity. Folate is one such ligand that is readily accessible, tiny, and has a high affinity for folate receptors. Chemotherapeutic drugs have disadvantages like resistance, disrupting healthy cell metabolism, and nonspecific targeting. Cancer immunotherapies include monoclonal antibodies, oncolytic viruses, cancer vaccines, and adoptive T cell transfer. Targeted drug delivery improves efficacy and reduces toxicity by increasing drug

concentration in specific areas. Passive targeting uses drug delivery systems in bone marrow vasculatures, while active targeting uses nanomedicines with peptide-modified nanomedicines. Despite significant improvements in diagnosis, long-lasting drug delivery, and therapy, cancer remains the leading cause of death worldwide. Infections, which already account for 20% of cancer cases and are anticipated to play a bigger role in the process of carcinogenesis, are projected to cause more cancer cases in the future.

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