A Review Article on the Basic Concepts of Drug Delivery Systems as Targeting Agents

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***Abstract*—Cancer represents the most life threatening disease worldwide where cells lose their normal regulatory mechanism that control their growth hence cells grow out of control resulting in a mass known as tumor. It shows complicated protocols of treatment, as the major limitation of most conventional anticancer therapy is the lack of tumor selectivity and killing of both normal and abnormal cells. Recently, several interests were introduced in the field of Drug Delivery Systems (DDS) in order to enhance the therapeutic effect and decrease the side effects of anticancer drugs. Several mechanisms have been introduced to moderate the effect of DDS, among them passive drug targeting, where the drug is incorporated into surface modified nanocarriers such as liposomes, niosomes, solid lipid Nanoparticles (NP) and Nanoemulsions (NE). Surface modification is achieved by increasing the hydrophilicity of the DDS since, it is known that hydrophobic surfaces tends to absorb high amount of proteins. Among hydrophilic polymer, PEG, PVA, dextran. However, PEG is the most frequently hydrophilic polymer applied for surface modification that increase the circulation time of nanocarriers and reduce the liver uptake compared to non-surface modified one. The Enhanced Permeability and Retention (EPR) effect is a phenomenon of tumor cells related to their anatomical and pathophysiological structure and their variations from normal tissues. EPR effect provides long-circulating PEG nanocarriers with a high opportunity to target tumor cells following systemic administration. In the current review a brief summary regarding nanocarriers and its mechanism as a drug targeting systems are discussed.**

***Index Term*—drug targeting, anticancer, nanocarriers, PEGylation**

I. Introduction

All the cells in our bodies have certain jobs to perform, normal cells divide in a normal way, they die when they damaged, and then they are replaced with new cells. Cancer is a disease in which cells start to grow out of control, uncoordinatedly and in accelerated way [1]. Such abnormal cell growth leads to formation of abnormal tissue called tumor. The cancer cells keep on growing and making new cells, these cells almost resemble the normal one [2].

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Cancer can be classified according to the site of origin; such as breast or liver cancer that originating from breast or liver. Or according to the cellular origin, into carcinoma, sarcoma and leukemia [3].

The incidence of developing cancer seems to be environmental as it depends largely on lifestyle and environment. Lifestyle choices as diet and obesity considered to be a cause for deaths every year. In addition, tobacco and alcohol consumption can cause mouth and throat cancer. On the other hand, changing our lifestyles will help to reduce the risk of developing cancers. Another factor that is considered as a risk factor for cancers is age, where cancer incidence is increased with age [4].

Cancer arises in tissue as a result of exposure to certain chemicals which known as carcinogens that cause genetic mutation which lead to carcinogenesis. Further, the exposure to UV radiation in rays of the sun is considered to increase the risk of cancer, where radiation may induce DNA mutation. Additionally, infectious agent such as bacteria, viruses and parasites were found to contribute in carcinogenic induction and finally cancer may be inherited.

It is well known that cancer arises due to mutations in cancer-susceptibility genes. Whenever a cell divides, another cell has to die in order to keep the total size the same. Cancer appears if the equilibrium between cell birth and cell death is shifted toward uncontrolled proliferation [5].

II. Types of Tumors

Although all tumors have certain characteristics as they are old or damaged cells, tumors could be divided into two main types, cancerous (malignant tumor) and non-cancerous one (benign Tumor) [6] as shown in Fig. 1.

A. Benign Tumor

It is not a cancerous tumor as it is unable to spread all over the body. Moreover, it is less risky and it could respond well to the treatment and in some cases treatment is not required. It is less likely to be recurrent. It may be caused due to inflammation, traumatic injury, undetected infection, exposure to certain toxins, diet or stress [7].

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B. Malignant Tumor

This type is cancerous which means that division occurs without control and it may extend to other body parts through lymph and blood. Initially, there may be no symptoms except appearance of painless lymph. The growth of tumor is being more rapidly than benign tumor and tumor treatment is a must. Malignant tumor may be occurred due to many causes such as poor diet, alcohol consumption, smoking, pollution and toxins [8].

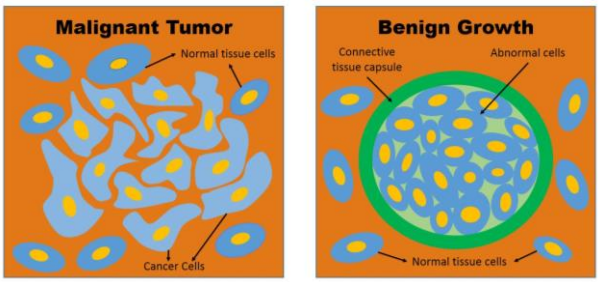

Figure 1. Enign versus malignant tumors.

The most common types of malignant tumors are:

1) Sarcoma: In connective tissue including muscles, fats and cartilage.
2) Carcinomas: In glands, tissue and organs as breast cancer, lung cancer.
3) Leukemia: In bone marrow and blood tissue.
4) Lymphoma: In the immune system cells.

III. Common Irregular Traits of Cancer Cell

All cancer cells have a common feature. They loss normal arrangement of cells, they develop changes in the cell membranes and they exhibit chromosomal abnormalities [9]. Three main features of cancer:

A. Excessive and Abnormal Cell Growth

Cancer cells grow and divide at rapid rate. They have abnormal membranes and morphology. The abnormality in cells can be progressive with a slow transition from normal cells to benign tumors then to malignant tumors.

B. Immortality

Immortality is a very common character in cancers. The cancer cells are considered to be immortal as they are able to live and divide for indefinite period of time [10].

C. Abnormal Cell Features

Cancer cells usually show much more variability in size, as they may be larger or smaller than normal cells. Moreover, cancer cells have an abnormal cell shape and abnormal shape for nucleus as well, where nucleus appears huge and darker. Cancer cells predominantly carry an irregular number of chromosomes that are disorderly arranged [11].

IV. Strategy for Cancer Treatment

The most common methods for cancer treatments are surgery, radiation, chemotherapy, hormonal therapy and immunotherapy (Table I).

A-Surgery is a strategy applied to take off the tumor when it is confined to the organ where it started, however surgery couldn't be used for all types of cancer.

B-Radiation treatment is also used to kill or decelerate the growth of cancer cells, it can be used alone or with surgery or chemotherapy.

C-Chemotherapy is the use of cytotoxic drugs in order to stop cancer cells or to slow their growth down. It may be given by IV or ingested as a pill or liquid. Because these drugs reach to almost all body parts, they are helpful for cancer that has spread [12].

Many different drugs are available as chemotherapy. These drugs can be used alone or in association for treating a wide variety of cancers. Chemotherapy is a treatment using anticancer or cytotoxic drugs which aim to destroy cancer cells. They may:

- Stop cancer cells from dividing and growing by interrupting the cell cycle
- Make cancer cells less able to grow and spread. One of the features that differentiate anticancer agents from other drugs is the frequency and intensity of adverse reactions that may happen at therapeutic doses. These side effects may be acute or chronic, self-limited, permanent, mild or life threatening [13]. Common toxicities encountered are gastrointestinal toxicity as nausea, vomiting and anorexia.

TABLE I. The Classical Classification of Anticancer Drugs

Category	Examples
I- Chemotherapy	1- Alkylating agents 2- Antimetabolites 3- Cytotoxic Antibiotics
II- Hormonal therapy	1- Steroids 2- Anti-estrogens 3- Anti-androgens 4- LH–RH analogs 5- Anti-aromatase agents
III- Immunotherapy	1- Interferon 2- Interleukin 2 3- Vaccines

V. Drug Targeting Strategies

Chemotherapy can be improved through anticancer drug delivery strategies. For a drug to give the expected therapeutic effect, an appropriate amount of the drug must be available at the site of action for specific period of time. However, the distribution of drugs to normal cell, where the drug action is not needed, as well as the cancer tissues is a source of side effects or toxicity. Moreover, to achieve the required effective concentration of the drug in a definite tissue, patient has to take the drug in considerable quantities, which will increase the cost of the therapy, and some of the drug will be wasted in normal tissues, that will give rise to many negative side-effects. Therefore, drug targeting which is delivering drugs only to the target organs, is very attractive and expected [14].

An ideal drug delivery system should have and achieve some of the following properties:

- The carrier should be nontoxic, biodegradable, biocompatible and physicochemically stable *in vivo* and *in vitro* [15].
- The effect of the drug prolonged due to a longer residence time in the plasma compared to the free drug.
- The cost of therapy; will be decreased as there is no need to administer drug in large quantity.
- Keeping the drug within the system till reaching to the target site, and releasing the drug at the target site at the appropriate rate.
- Interacting selectively with the specific cells of the target tissue by introducing specific, biologically recognized structural units.
- Increasing the drug concentration in the required tissue without negative side effects.
- Improving the stability of the drug against difficult condition of the surrounding environment.
- The drug quantity required to achieve the therapeutic effect may be greatly reduced.
- Carrier used should readily be discarded from the body without causing any problem [16].

Targeted drug delivery system usually contain:

a) targets which refers to specific organ or a cell, that require a treatment.
b) carrier system which is the special molecule or system that required for transporting or loading the drug up to the selected targeted sites [17].

A. *Passive Targeting*

Tumors are characterized by poorly differentiated, defective vascular architecture, impaired lymphatic drainage-recovery system, irregular shape, heterogeneity and high density as illustrated in Fig. 2.

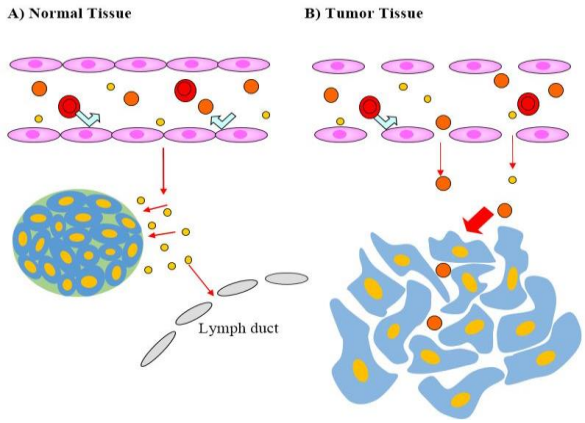

Figure 2. Schematic representation illustrating a comparison between (A) intact vasculature and (B) leaky vasculature that allow EPR effect or passive targeting.

This abnormal vasculature plays an essential role for an EPR effect (Enhanced Permeability and Retention effect) [18]. This type of targeting requires drug delivery systems to be long-circulating (i.e., drug carrier will stay in the blood for long time, accumulate in pathological target sites that have leaky vasculature more than they do in normal cells). Relatively large particles, can leave the vascular bed and accumulate inside the interstitial space [19]. The most usual way to keep drug carriers in the blood for long period is to "mask" them and make surface modification with certain water-soluble polymers such as Polyethylene Glycol (PEG) that has been proven to be more effective so far [20]. Modification may also be done with polysaccharides, poly(acrylamide), and poly (vinyl alcohol). These polymers effectively prevent the opsonization of drug carriers and their clearance by the reticuloendothelial system.

B. *Active Targeting (Magic Bullet)*

Active targeting involves drug delivery to a specific site based on molecular recognition [21], where nanocarrier loaded with the drug is modified with the moieties of a specific ligand that can recognize certain binding sites on the cell surface. As a result, the carrier remains attached to the cell surface and releases its drug load there or can be internalized bringing the drug inside target cells [22]. Fig. 3 shows a schematic representation of active targeting mechanism.

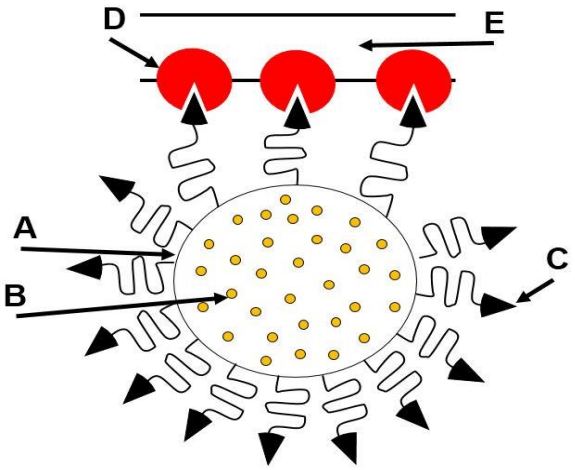

Figure 3. Schematics representation illustrating the mechanism of active targeting. (A) nanocarrier (B) the drug (C) ligand (D) cell surface (E) binding sites.

VI. Pharmaceutical Drug Carriers Used for Targeted Delivery

Different drug delivery and targeting drug delivery systems are developed or under development. Their application intended to diminish drug degradation upon administration, prevent unfavorable side-effects, increase the bioavailability of the drug and the amount of the drug accumulated in the pathological area. Delivery systems modify and adjust the pharmacokinetics of the drug by changing its elimination and distribution profiles.

A. *Liposome*

Liposome is a drug delivery system that can limit the random diffusion of the drug in the body [23]. It may be a lipid bilayer structure that encases an inside fluid volume. It is of spherical shape created from cholesterol and phospholipid [24]. Liposomes increased the efficacy of the drug and increased the stability via encapsulation. Moreover, it can reduce the toxicity of the encapsulated

drug. It can ameliorate the solubility of lipophilic and amphiphilic loaded drugs [25]**.** Liposomes are versatile, efficient and it is the most extensively studied type of delivery systems [26].

B. Noisome

They are closed bilayer vesicles formed from the hydration of cholesterol and nonionic surfactant [27]. They accumulate in the tumor cells in the same manner as liposomes. The therapeutic performance of the drug molecules could be improved by retarding its clearance from the circulation, keeping the drug from biological environment and limiting effects to target cells. Niosomes could reach the target site through oral, parenteral and topical routes [28]. They ameliorate the oral bioavailability of drugs that poorly absorbed and could enhance skin penetration of certain drugs. Niosomes are more preferable than liposomes because of its chemical stability [29].

C. Nanoparticle (NPs)

Nanoparticles are one of the novel drug delivery systems, it is solid with submicron size usually less than 100 nm in diameter. Nanoparticle indicates both nanosphares and nanocapsules. Nanospheres are matrix system in which the drug is dispersed uniformly however nanocapsules are the systems in which the drug is enclosed within a polymeric membrane [30]. Nanoparticles (NPs) may incorporate insoluble drugs or extremely toxic drugs through nanotechnology. *In vivo* investigation of drugs in nanoparticles, showed that the antitumor drugs may be selectively transferred to the tumor tissues, which results in raising the drug concentration and delay its release, keeping its effect for a long time [31].

D. Nanoemulsion

Nanoemulsions are another type of drug carrier. They are thermodynamically stable system composed of two immiscible liquids, water and oil, that mixed together using appropriate surfactant to form a single phase. Nanoemulsions possess a great stability in due to their small droplet size. It considered to be a good choice as a drug carrier especially for poor water soluble drugs. It is applied in different areas such as in cancer treatment, drug targeting, vehicle for transdermal drug delivery, etc. [32]. Their efficacy in cancer therapy is attributed to their small particle size, high loading capacity and good stability. They are promising in application as they have slower and more sustained drug release so they are more efficient in preventing and treating tumor [33].

E. Soluble Polymers

Since water-soluble polymer-drug conjugates reveal good water solubility, long half-life and potentiate the anti-tumor effects by targeting the drug at the required site of action, such macromolecular therapeutics have improved efficacy and enhanced safety at lower doses. Anticancer-drug polymer conjugates can be applied in two targeting ways: passive and active. Both natural and synthetic polymers have been used as drug carriers, and numerous bioconjugates have been approved clinically or are under clinical trials. Whereas clinically useful anti-tumor activity has been accomplished via passive targeting, further selectivity could be achieved by active targeting. Furthermore, connecting the targeting moieties to the polymer backbone can employ the variations between cancer and normal cells by means of selective receptor-mediated endocytosis. The advanced polymer chemistry allows the development of tailor-made conjugates in which soluble synthetic polymers are conjugated with targeting moiety, forming drug loaded carrier molecules [19].

F. Monoclonal Antibody

Monoclonal Antibodies (MAbs) bind to particular markers on the surface of cancer cells show substitutional therapy that is tumor specific and consequently less toxic. In spite of the fact that they are highly selective, very few MAbs are therapeutically useful. The connection of monoclonal antibodies to highly cytotoxic drugs can be regarded as a mean of (a) giving very high tumor selectivity to cytotoxic drugs which are very toxic to be utilized alone. (b) providing cell-killing capability to MAbs that are tumor-specific but not adequately cytotoxic [34]. Obstacles for using MAbs in cancer treatment is that the distribution of antigen of malignant cells is highly heterogeneous, since some cells may show tumor antigens, whereas others do not. MAbs may not reach the tumor tissues as the tumor blood flow is not always optimal. More important point is high cost of these antibodies that considered to be a great obstacle for the use of these drugs [35].

G. Polymeric Micelles

Polymeric micelles have common features like higher stability, more prominent cargo capacity, non-toxicity and controlled drug release [36]. They are particles with nano-size, composed of polymer chains. They are usually formed spontaneously by self-assembly, due to hydrophobic interactions between polymer segments. These types of micelles called core-shell structure. The core of the micelles is the hydrophobic part of the nanoparticles and has the ability to contain lipophilic molecules such as therapeutic drugs, while the shell has surface to the aqueous solution so this make the nanoparticles more stable in the solution. Polymeric micelles are considered to be the best alternative drug carriers in comparison to other micellar systems.

H. Ipoprotein

Lipoproteins are biochemical assembly that contain proteins and lipids. They have attracted great interest in recent years for their importance as a carrier for drug targeting. After isolating lipoprotein particles from the blood, drugs can be loaded onto them through many ways. The drug-loaded lipoproteins can be adjusted by the attachment of different ligands that target the particles to

specific tissue or organ within the body. Lipoproteins are endogenous lipid particles containing apoproteins, where lipophilic drug can be integratd into their lipid moiety [37].

VII. Interaction of Carriers with Blood Proteins

A. Opsonization

Some proteins that adsorb onto the surface of the particle after intravenous administration are known to facilitate the phagocytosis of the particles. These proteins promoting the phagocytosis are known as opsonins. Opsonization is the process by which opsonin will adsorb on the surface of particles after intravenous administration, promote recognition and uptake by the RES through receptor-mediated phagocytosis or endocytosis as it being more visible to phagocytic cells [38]**.** Furthermore, opsonization refers to an immune process where particles such as microorganism are targeted for destruction by an immune cell known as a phagocyte and removed from the circulation within seconds to minutes [39]. The opsonization is a way of recognizing the invading particle to the phagocyte. Without opsonization the recognition and destruction of invading agents would be difficult.

Phagocytosis can occur after opsonization, which is the process of engulfing and removing the foreign materials from the bloodstream. The mechanism by which this process is activated is very complicated and not fully understood yet. Immunoglobulins and components of the complement system such as C_3, C_4, and C_5 are known to be common opsonins and has been suggested to be mainly responsible for the clearance of particles via opsonization [40]. They will attack foreign particles entering the systemic circulation promoting their lysis or removal by phagocyte through receptor mediated recognition of activated C_3 fragments. These phagocytes may be circulating as macrophage or resident as Kupffer cells and they include the complement-responsive elements of RES. Although the natural role of opsonization is to protect the body from nano and foreign systems, this process will also promote the removal of circulating drug nanocarriers which considered to be a great obstacle to achieve the required therapeutic drug concentrations [39]. Interaction of opsonin and nanocarriers in the blood occurs by van der Waals forces, electrostatic forces and hydrophobic/hydrophilic forces. Thus, the characteristic traits of the nanocarriers surface have a remarkable role in the opsonisation process as hydrophilic and particles with neutral charge undergo less opsonisation than hydrophobic and charged particles due the enhanced adsorbability of blood serum proteins on the surface of hydrophobic carriers [38].

Action of complement system can be summarized as follows:

1) Lysis of bacterial cell wall
2) Stimulation of histamine release from tissue cells and leukocytes, hence increasing the capillary permeability.
3) Coating the surface of particles making them recognizable to neutrophils and macrophages.

The complement cascade pathway is a process in the blood that helps the immune system to eliminate foreign bodies. The proteins of the complement system are circulating in the plasma in an inefficient form and the system is activated when the cascade is initiated. One more important function of the complement system for the removal of invading particles is the assembly of C5b-9 complexes (membrane attack complex: MAC), which produces a lytic pore, on the surface of particles [41].

1) Pathways for complement activation

The two major pathways for activating the complement are the classical pathway, which is activated by specific types of antibodies tied with antigens, and the alternative pathway, which is activated on microbial cell surfaces with the lack of antibody. The pathway is triggered when the C_3b protein directly binds a microbe. The two pathways of complement activation vary in method of initiation, but both of them result in the generation of enzyme complexes that have the power to cleave and activate the complement protein C_3.

2) Other serum proteins acting as opsonins

- Immunoglobulin:
  Five different groups of immunoglobulins are available, IgG, IgA, IgD, IgE and IgM. IgG is a predominant one as it represents about 70% of total immunoglobulins and play a vital role in elimination of foreign particles by acting as opsonin [42].
- Lipoprotein
  like VLDL, LDL and HDL may act as an opsonin enhancing the phagocytosis. Many types of apolipoproteins were adsorbed onto liposomal surface either. Apo E is one of different apolipoproteins which is known to play a pivotal role in liposomal uptake by the liver, especially by hepatocytes expressing the receptor for apo E [38], [43].

B. Dysopsonization

One of the strategies to avoid opsonization is extending of the particle persistence in the bloodstream for longer time. This strategy is achieved by formulating Stealth systems or long circulating nanocarriers which can be acquired by covering their surfaces with hydrophilic polymers that alter opsonization [38].

The presence of polyethylene glycol (PEG), which is the polymer of choice to form stealth nanocarriers, at the surface of the carrier has a great role in extending the circulation lifetime of the vehicle and preventing rapid clearance [44]. The extended circulation lifetime that the polymer confers has been attributed to reducing or preventing protein adsorption [45]. It was noticed that the formation of weak complexes between PEG and albumin may cause them to be like native albumin, resulting in a “chameleon” effect that prevents interactions of PEG with other plasma proteins [46].

Dysopsonins are naturally occurring substances like proteins that can increase blood circulation time and are recognized by specific receptors. Dysopsonins are also

act to inhibit phagocytic ingestion, among them are IgA, albumin and others.

1) Albumin

Albumin is a protein found in the blood. It is the most plentiful protein in serum, as its concentration is around 5% (w/v). Its function is to transport both endogenous and exogenous ligands like hormones and fatty acids to tissues. It considered to be one of a dysopsonin. Even though albumin adsorption can protect drug carrier from supplemental opsonization, albumin can be easily substituted by other proteins that have higher affinities and this will result in limiting the dysopsonin effect of albumin. In order to avoid this replacement, albumin can be bound directly to NPs or drugs. Albumin-bound NPs greatly consolidate the blood circulation time of the drug [47]. The researchers concluded that albumin might provide dysopsonin-like activity by inhibiting the association of opsonins to the nanocarrier surface [48].

2) IgA

IgA is an antibody that plays an important role in the immune function. IgA is regarded as a dysopsonin for the microorganisms as it is a poor activator of the complement system [49]. It prevents the adherence of microorganisms to epithelial surfaces as well as their ingestion by neutrophils and macrophages. Additionally, it was suggested that α1-acid glycoprotein could inhibit phagocytosis of pathogens or particles in vitro.

VIII. Conclusion

Nanotechnology and its applications receive a great attention especially in the field of cancer therapy. Nanocarriers considered to be promising tools for cancer treatment in order to avoid the side effects of anticancer agents. Regardless of the considerable achievement that being made in developing drug delivery systems for cancer therapy, a number of obstacles still need to be handled. Certain modifications for nanocarrier surfaces via chemically or physically active components have been done in order to permit the delivery of different drugs. Subsequently, the drug carriers can be passively or actively targeted for cancer tissue.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

The review article draft was originally written by Heba S.Elswedy. The final version was revised and languish edited by Bandar E. Al Dubiab , Mahmoud M Mahdy and Hanan M Elnahas; all authors had approved the final version.

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