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Nanoparticles and target Drug delivery for cancer treatment: A Comprehensive review

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Abstract

In the healthcare industry, the biggest challenges are cancer. However, there are several drugs are available for the treatment of cancer. In these treatments cure cancer affecting the collateral toxicity to healthy cells. In addition to the drug delivery systems in cancer have many barriers such as immune clearance or hepatic, renal. Thus, to improve treatment and overcome these problems the nanoparticle-loaded drug is one the solution. Moreover, the nanomedicine opens a new era in the healthcare industry as an effective drug delivery system. The nanoparticle drug delivery has significant characteristics for treatments such as less toxicity, high loading capacity, and stability of the drug. This review aims to present the conventional cancer treatment and elaborate on the nanoparticle-loaded drug delivery system to overcome the side effects of the conventional treatment.

Keywords: Targeted Drug delivery systems, Nanoparticles, cancer treatment.

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1. Introduction

In the recent worldwide data base of cancer clearly state that cancer diseases are one of the major factors for the deaths and 60092 deaths were reported and 168870 are new cases enrolled in the cancer in the year of 2017. In addition to this data based in next 20 years the 70% increase the patient of cancer (1). There are many treatments of the cancer recently available such as surgery, chemotherapy and radiation but such treatments are not most effective because of its side effects. Weinberg et. al. did the research and they suggested the six different type of characteristics to differentiate the tumor and normal tissue in body therefore some alternative option should be approach for better treatment. The six different characteristics such as, inducing angiogenesis, metastasis and invasion, resisting cell death, signaling, enabling replicative immortality and evading growth suppressors (2). Based on these characteristics the new development and investigation have been significantly carried out and found the new methods for the treatment. Such new development in the cancer treatment technology known as nanomedicine or Nano technology. These nanomaterial have 1 to 100 nm material size, favorable drug release Profiles, modification of surface and high surface-to-volume ratios characteristics and it enhanced the current treatment remedies Such as rapid drug clearance, limited targeting, low specificity and biodegradation (3, 4).

Moreover, the targeted drug delivery methods for the cancer treatment are most viable and improve the treatment effects in comparison to the existing convectional treatment and reduces the adverse effects of convection treatment. Therefore, the systematic and nonspecific target drug delivery systems lead the rapid elimination and administration of highest tolerable dose of drug thus reduces the toxicity. In general, targeted drug delivery system can be approach by the inorganic and organic particles. The nanogels, polymers, liposomes, dendrimers and micelles are the organic particles and its application as target drug delivery systems.

Observing the recent advancement and trends for the cancer treatment nanosized materials are most effective for the tumor treatment (3). As we discussed above the

nanoparticles have nanosized material which can be embedded with the genes, drug and imaging agents (2). The nanoparticles are directly delivered high doses of therapeutic factors to the tumor cells at that time the normal cells of he body are cured because these particles are by passing the normal cells. The nanoparticle scaffold structure allowed the contrast agent and drug attachment. In addition to this nanoparticle surface enables specific delivery and biodistribution through conjugation with ligands (3). Hence the nanoparticle resolved problems of conventional treatment, unwanted adverse effects, biodistribution, including non-specific and drug resistance.

The research development of the nanoparticles is currently in the clinical trail from last two decades. Also, the modifications in various v features of the nanoparticles were improve the potential of the cancer treatment. The circulation half-life of therapeutics could be improved by nanocarriers thus the drug accumulation at tumor location would be enhanced (4, 5). In nanoparticles the particles fate is depends on the size therefore it is an important factor. However, nanoparticles with the 100nm are clear from circulation by phagocytic cells (6, 7) and the smaller nanoparticles less than 7nm fall into urinary excretion renal filtration (8, 9). In addition to this internalization into the cancer cells would be possible through surface positive charge particles. polyethylene glycol adding on surface as polymer would enhance the circulation life of the particles. Thus, surface modification plays significant role in improvement in internalization of cancer cell and circulating time. Therefore, active targeting (specific ligand on surface) can overcome the problems and provide better treatment (10).

Therapeutic NPs

During the last two decades, researchers investigated to use several NPs in the wide variety of pathologic conditions (11). Liposomes with a lipid scaffold structure which are consist of self-assembled phospholipids into bilayers with spherical shape (12). Liposomes can encapsulate the hydrophilic therapeutic factors within the vesicles whereas hydrophobic therapeutic factors within the lipid bilayer (13). Recently, there are many liposome-based anti-cancer compounds accessible for clinical practice (14). Nanostructured lipid carriers (NLC) can potently be affected by tumor cells and reveal advantages such as high drug loading potential, controlled drug release, increasing drug stability, and the ease of large-scale generation (15). Solid Lipid NPs (SLNs) are non-toxic nanocarriers which can carry both the hydrophilic and lipophilic drugs. FDA approved Poly (lactic-co-glycolic acid) (PLGA) for drug delivery which is a biodegradable polymeric NP (16). Dendrimers used for both the diagnostic and therapeutic purposes characterized by the generation of monomers (G) added to the main core (17). Iron oxide NPs can be visualized by Magnetic Resonance Imaging (MRI), used for imaging purposes in the various tumor (18). Michael Farady identified Gold NPs which can be easily modified by amine and thiol groups for tumor-specific targeting. (19).

2. Types of nanoparticles

Protein-Drug Conjugated nanoparticles

The proteins directly conjugated with the drug molecules that formation labeled as Protein-drug conjugated nanoparticles. As they are coming in the cell, the connection becomes a typically biodegradable which is form between the protein and the drug. As the biodegradable connection has been readily destroyed by proteases and redox-altering agents which are develop in blood to lead to premature release of the drug. Protein-drug conjugated system with their connection helps to stay in the place which is helpful to overcome this barrier. This system keeps linkers in the place until the nanoparticles reach the target site. With the help of this system, the toxic effect of cytotoxic drug molecules can be decreased as the system permits more specific and controllable drug delivery of the treatment of the body (20). Characteristically, Protein-drug conjugated nanoparticles are allowing the nanoparticles in vivo to have a long half-life as they are small in size (10nm), resulting from targeting tumor site its delivery is being helped (21, 22). In recent times, Protein-drug conjugated nanoparticles added antibody proteins to improving their targeting ability (23). There are some drug structural sensitivity creating difficulty to attach to a protein base which is a fundamental issue with protein-based nanoparticles while several drugs are not appropriate for the Protein-Drug Conjugated nanoparticles drug delivery system (24, 25).

Liposomal Nanoparticles

Liposome nanoparticles made up by using lipid bilayers as they are spherical nanoparticles. To develop nanoparticles immediately, there are strong spheres approximetly between 50 and 500 nm, thus water or other hydrophilic liquids has been added by amphiphilic lipid. Basically, drug dissolved in the liquid through this procedure to the encapsulation of hydrophilic drug molecules, used for formation of the nanoparticles. Hydrophobic and amphiphilic drugs can be encapsulated by direct accumulation to the lipid solution. The structure is develped before the nanoparticles formation which is a leading layer between the lipid bilayers (20, 26). The encapsulated drugs may be released by thermosensitive liposomes at the exact temperature (27). The benefit to using liposomes which allows to the delivery drug at targeted sites. The energy sources located at those targeted sites such as high-intensity ultrasound, microwaves, and radio frequencies (28).

Polymeric Nanoparticles

Polymeric nanoparticles are encompassed of synthetic polymers which are allowing many key properties customization, for instance, as molecular weight, biodegradability, and hydrophobicity. The encapsulate drug molecules have been designed by a variety of efficient methods. Polymeric nanoparticles are characteristically entailed of dense matrices with well-known degradation curves. These nanoparticles allow the drug release easier to manipulate in comparison to many other nanoparticle drug delivery system (20). There is a problem with using polymeric nanoparticles which include the limited shape and wide size distribution.

Nanoparticles size may be different which may be generated during synthesis; characteristically it is spherical. The latest approach is particle replication in nonwetting templates. This approach allows for the creation of uniform polymeric nanoparticles, permitting the customization of properties, for instance, shape and size (29).

Dendrimeric Nanoparticles

Dendrimeric nanoparticles are consists of dendrimers. These dendrimers are spherical macromolecules which are developing from a central point. Dendrimeric nanoparticles are created layer by layer. The early core incorporated onto the previous layer before branches are allowed to form. The size and degree of branching of the dendrimers can easily be manipulated by using specific initiator cores, which allows for the polydispersity of the nanoparticles to minimized. The molecular weight, size, branch, density, flexibility, and water solubility can be specified with careful planning the arrangement of cores and branching units (20).

Hydrogels

Hydrogels are cross-linked three-dimensional networks of water-soluble polymers which can retain fluid in large quantities. Majority of synthetic hydrogels are not biodegradable. However, hydrogels are enzymatic, hydrolytic, and stimuli-responsive components. Hydrogel can be added into the hydrogel matrix in order to create nanoparticles. These nanoparticles are degradable under certain conditions. Their fluid retainment is the exclusivity of hydrogels. The high water content is very similar to biological tissues. This content is reducing tension when introduced to tissue and making this nanoparticle biocompatible (30). The porosity of the hydrogel can be adjusted to control drug loading and release rates by controlling the amount of cross-linking in the hydrogel matrix (20).

Other nanoparticle platforms

Gold is a well-characterized nanoparticle which is inorganic and metallic in nature. Since a long time, Gold broadly used for both detection and direct cancer therapy with and without drug loading. For the detection, the strong optical absorbance of gold allows it, while its photothermic properties are well suitable as an anticancer therapy (20).

3. Nanocarrier Properties:

Physico-chemical properties

The nanomaterials can modify in size, shape, and surface characteristics. This modification can help to treat specific tumors which are available for cancer research. The tumor tissue, size of nanocarriers are important for travel through the bloodstream and consequent delivery. The smaller nanoparticle can accumulate easily in the leaky blood vessels of the tumors and extravasate into normal tissues, whereas larger nanoparticles cannot excavate as easily as smaller nanoparticles, therefore the distribution of the nanoparticles in the bloodstream is highly variable (31). The nanoparticle optimization and nanocarriers shape may help improve specific uptake into tumor tissue and impact fluid dynamics respectively, consequently influence uptake. Presently, the spherical nanocarriers are commonly used than that of the nonspherical variety because of challenges in synthesis and testing (32). It has observed that the charge of nanocarriers affects their stability and distribution in the blood, as positively charged nanoparticles most effectively target tumor vessels. Conversely, a switch to a neutral charge after extravasation permits quicker diffusion of the nanoparticles to the tumor tissue (8).

Solubility, degradation, and clearance

Drugs may be eliminated from the bloodstream before reaching tumor tissue due to their poor water solubility. The hydrophilic nanoparticles encapsulated these drugs to improve their solubility. The use of hydrophilic nanoparticles may improve their bio-availability in vivo (33). Consequently, it allows for more effective delivery (3). The hydrophobic materials have been recognized by the reticulo-endothelial system (RES) as a foreign substance; RES eliminates hydrophobic materials from the bloodstream through the liver or the spleen. Monocytes and macrophages are more easily recognize foreign materials which are coated with opsonin proteins (9). Opsonization of hydrophobic molecules. Opsonization of hydrophobic molecules can diminish capability to reach the tumor tissue and trigger inflammation subsequently the secretion of cytokines from phagocytic cells (6, 7). This improvement in bioavailability increase capability of the drug to circulate in the blood for a longer period, preventing degradation before reaching the tissue of interest.

Targeting

To reach tumor tissue, It has observed modify nanocarriers to utilize passive and active targeting mechanisms shown in figure 1. Passively accumulate nanoparticles due to enhanced permeability and retention (EPR) (34) effect, in the leaky blood vasculature exhibited by tumors without any surface modifications. However, it cannot eliminate the potential of nanocarriers building up in tissues. These tissues usually have fenestrated blood vessels, for instance, the liver or the spleen (3). The attachment of ligands to the surface of the nanocarriers utilize in active targeting, have high specificity to receptors and other cancer-specific targets which are overexpressed on the surface of tumor cells, such as glycans (35-37).

Stimuli-responsive and triggered release systems

The stimuli-responsive systems utilize to reduce non-specific exposure to chemotherapeutic drugs mentioned in figure 1. Internal and external both stimuli can evoke a change in the nanocarriers to trigger the release of drugs. Internal stimuli are changes in pH, redox, ionic strength, and stress in target tissues whereas external stimuli are temperature, light, ultrasound, magnetic force, and electric fields (3).

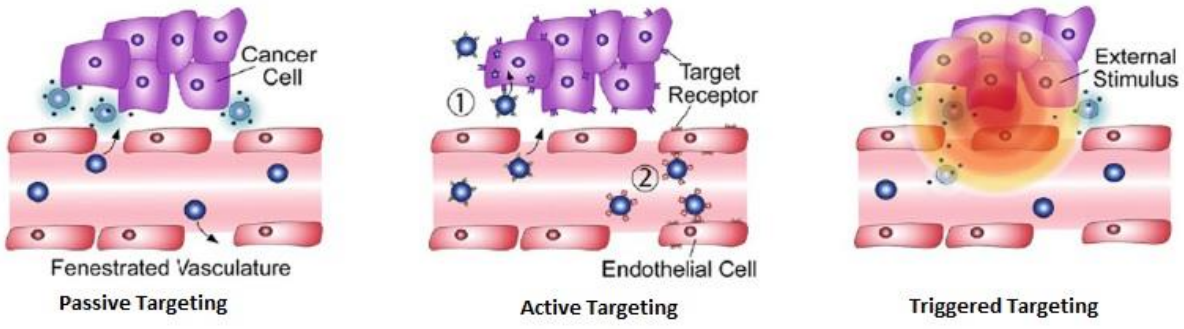

Figure 2. Types of targeting for nanoparticle delivery to tumor tissue (3).

Combination therapy and theranostics

The nanomedicines carry multiple therapeutic agents permits an increase in their capacity to improve treatment. Bortezomib and doxorubicin co-loaded nanoparticles were shown to exhibit a synergistic antitumor effect on ovarian cancer (38). The investigate stimuli-responsive systems utilization with targeting ligands. The chemotherapeutic drugs delivery successfully is often dependent on the properties of the biological barriers.

4. Biological barriers to effective drug delivery

Reticuloendothelial system

The reticuloendothelial system (RES) includes both cellular and noncellular components, also known as the mononuclear phagocyte system (MPS). Phagocytic cells bind with nanoparticles which allow a release of cytokines. It leads to increase nanoparticle clearance from the bloodstream and local inflammation of tissue (7). The macromolecules may also bind to the surface of the nanoparticles to create a "biomolecular corona" around the nanoparticles. Macromolecules are proteins, lipids, and others. Nanoparticles surface modifications may allow escape from the RES and prolong their circulation time in the bloodstream till preventing damage of healthy tissue. Zwitterionic ligands, for instance, cysteine and glutathione or PEGylation involve modification (39, 40). Ligands such as CD47-SIRPα use to create signals which may inhibit phagocytic clearance (41). Nanoparticles toxicity to RES organ system should also be considered when designing their construct.

Renal System

The kidney function is to filter circulating blood. The primary objective of designing nanoparticles are defined barriers which responsible for filtering circulating blood in the kidney. Nanoparticles must pass a thick layer of extracellular matrix; a glomerular basement membrane sits between the capillary endothelium and podocytes which permit clearance for 2-8 nm particles after passing through the fenestrated endothelium with 70-100 nm pores (7). Proteins such as nephrin and CD-2 associated protein regulate the opening of slit diaphragms that situated between epithelial podocyte extensions that usually allow the passage of water and small molecules (42). Characteristics such as size, charge, and shape affect the clearance of nanoparticles in kidneys. The cationic nanoparticles of a 6-8nm display more massive clearance than negative charged or neutral of the same size. The exhibit take place as glomerular basement membrane is negatively charged (43). Nanoparticle efficacy may be compromised while reducing nanoparticle size may enhance renal clearance. Kidney clear multi-stage, biodegradable nanoparticles which dissolve into smaller particles, may be active (44).

Blood-brain barrier

The blood-brain barrier (BBB) is a structure of the brain which is very challenging treat brain cancers. The characteristics of BBB that it only allows passage of less than 2% molecules, including ions, nutrients, specific peptides, protien, and leukocytes (45, 46). There is a tight juction which linked endothelial cells. The endothelial cells are enclosed by astrocytic cells, basal lamina, pericytes, and microglia. These structures are consisting of the barrier. It has observed several methods which is currently used for increasing penetration. These methods are direct intervention into the brain, for instance, intra-verntricular or intracerebral injection, infusion, and implantation. It may increasing risk of toxicity and non-uniform drug dispersals (7). There passing through blood-brain barrier is a challenge which depen on nanoparticle size and charge, most essential. According to a study which shows the result and confirmation that nanoparticles are favored for transport which has 20-70 nm diameter (47, 48). It has been shown that neutral and anionic nanoparticles use in less neurotoxicity than cationic nanoparticles for an in situ perfusion study of rat brains (49). Nanoparticles comprising metals, for instance, copper, silver, and aluminum which may destroy the BBB and develop neurotoxicity. Nanomedicine can accumulate gratuitously in the brain and develop toxic condition for short-term and long-term. Neverthless, nanoparticles are reaching the brain which may be challenge to targeting for brain cancers under nanotherapy (50). Designing therapies which reduce activation of microglial cells may be suitable in reducing neurotoxic effects (7).

Pathophysiological barriers in cancer

The phenomenon which is called the enhanced permeability and retention (EPR) effect, which leaky vasculature rich in fenestrations and poor in pericyte coverage are tumor tissue characteristics. This phenomenon used for passive targeting of nanoparticles to

tumor tissue. However, deeper penetration into tumor which is frequently controlled because of the tumor microenvironment heterogeneity (51). Along with tumor vasculature, composition and structure of the extracellular matrix are highly variable and dependent on cancer type, location, and progression state, accompanied by patient-specific characteristics (7). Recently studied methods that to increase nanoparticle into the tumor bed. Smaller nanoparticles use may permit to enhance passage through the vasculature and deeper penetration into the tumor (52). The majority materials are using to create nanoparticles for drug delivery are proteins, liposomes, polymers, polymer-lipid hybrids, dendrimers, phase change materials, and inorganic materials.

5. Conclusion

In world the advancement in the nanomedicine plays the significant role in the drug delivery field. Target drug delivery system allowed drug delivery at the desired location therefore it alters the biodistribution and pharmacokinetics of the drugs. In addition to this, the nanoparticles are the replacement of the convectional particles. However, it is in the observation through this review the nanoparticles have many options in the design and functions with effective potential therefore drug delivery could be executing properly and effectively apply. On the other side the nanoparticle-based treatment is not the miracle to cure the diseases. There are many challenges for the selection of the drug and choosing the right surface marker.

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Conflict of interest

The authors declare that there is no conflict of interest, financial or otherwise.

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