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Therapeutic Nanoparticles for Drug Delivery In Cancer

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ABSTRACT:
Nanoparticles provide a new method for delivering cancer drugs. To increase the biodistribution of cancer drugs, nanoparticles have been designed with optimal properties of size and surface to increase their circulation time in the bloodstream. The new technology offers new opportunities for targeted delivery of high concentrations of drugs to cancer cells with reduced injury to normal cells. Nanoparticles have the advantage of targeting cancer by simply being accumulated and entrapped in tumors (passive targeting). In addition to this passive targeting mechanism, active targeting strategies using ligands or antibodies directed against selected tumor targets amplify the specificity of these therapeutic nanoparticles. Nanoparticles have the ability to accumulate in cells without being recognized by P-glycoprotein, one of the main mediators of multidrug resistance, resulting in the increased intracellular concentration of drugs. It is still
Necessary to conduct more research to overcome the limitations of traditional anticancer therapy. This review focuses on the potential of nanoparticle delivery system
in cancer treatment and future perspectives.
Keywords: Nanoparticles, drug delivery, tumor targeting, cancer, therapeutic.

I. INTRODUCTION:

The application of nanotechnology to medicine aims to overcome problems related to diseases, at the nanoscale where most of the biological molecules exist and operate. Today, there is a strong focus on nanotechnology application to cancer. Cancer Nanotechnology is a new field of interdisciplinary research cutting across biology, chemistry, engineering and medicine aiming to lead major advances in cancer detection, diagnosis and treatment. Nanoparticles are constructed to exploit the morphology and development of cancer, such as rapid proliferation of cells, the expression of antigens, and leaky vasculature, to enable the detection and treatment of individual cancer cells. [1] Nanoparticles can overcome biological barriers. They can accumulate preferentially in tumors and can recognize single cancer cells in the presence of their surroundings. A nanoparticle serving in anticancer therapy may contain lipids, natural and synthetic polymers, or a combination of both. The majority of synthetic polymers used to produce nanoparticles for drug delivery are biodegradable. [2]

Contemporary cancer therapy, particularly with respect to drug delivery, has begun an evolution from traditional methodology. Part of this change is based on the need to increase the therapeutic index of chemotherapy drugs. Although cancer cells are inherently more vulnerable than normal cells to the effect of chemotherapy agents. Drugs are nonselective and can cause injury to normal tissues. Indeed, it is the toxicity of normal cells that constrains dose and frequency, both important factors in the persistence of cancer cells after completion of chemotherapy treatment. Attempts are now focused on efforts to kill cancer cells by more specific targeting while sparing normal cells. To achieve these goals, the focus is on the development of novel carriers for both existing and new drugs and defining better therapeutic targets relative to the molecular changes in the cancer cells, their vasculature, and the related stroma.[11] In addition to being more effective, therapeutic nanoparticle formulations have the advantage of causing prolonged circulation times and decreased distribution volumes as their renal excretion is reduced. As a result, drug molecules accumulate less in healthy tissues, which leads to fewer side effects, while they are better able to accumulate around the pathological site, thereby increasing their therapeutic efficacy.[12]

The purpose of this review will be to outline the types and characteristics of nanoparticles and how nanoparticles are used as a drug delivery system for attacking cancer cells. Following that, we will discuss the therapeutic efficacy and application of nanoparticles as well as

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what their Contributions will be to future cancer therapy.

Characteristic of Nanoparticles:

Nanoparticles must have the ability to remain in the bloodstream for a Considerable time without being eliminated For effective delivery of drugs to the targeted tumor tissue. Conventional surface particles and non-modified nanoparticles are usually caught in the circulation by the reticuloendothelial system (RES), such as the liver and the spleen, depending on their size and surface characteristics.[8] The two major factors affecting their uptake by tumor cells and recognition by the RES are particle size and surface characteristics.

Size. The size of nanoparticles used in a drug delivery system should be small enough to escape capture by fixed macrophages that are lodged in the reticuloendothelial system, such as the liver and spleen but should be large enough to prevent their rapid leakage into blood capillaries.[8] As for the nanoparticles' size, unlike normal blood vessels, the gap junctions between adjacent endothelial cells in tumor tissues have been estimated to be 100–600 nm

Therefore, it is hypothesized that, for adequate tumor extravasation and accumulation, the most favorable size of nanoparticles is smaller than 100 nm.[9]

Surface. Surface characteristics of nanoparticles are an important factor for determining their lifespan and destiny during circulation relating to their capture by macrophages.[8] Nanocarriers with hydrophilic surfaces have prolonged circulation times in the bloodstream due to decreased clearance by RES. This can be achieved by modifying the surface of nanoparticles with the addition of a hydrophilic polymer.[9] This can be achieved in two ways: coating the surface of Nanoparticles with a hydrophilic polymer, such as polyethylene glycol (PEG) are able to confer 'stealth' properties to nanoparticles, presumably because the PEGylation of the nanoparticle surface prevents opsonin binding by reducing the protein interactions and hence PEG would improve the colloidal stability and prevent nanoparticle capture by the RES, increasing their circulation time and hence their accumulation at the tumor site. Alternatively, nanoparticles can be formed from block copolymers with hydrophilic and hydrophobic domains. It is well known that positively charged nanoparticles are easily taken up by cells, however they produce important immune reactions.[4,9]

Evolving approach to Drug Delivery:

Recently, there have been huge developments in the area of administration systems to supply therapeutic agents or natural active compounds at its target location for the treatment of various diseases.[7] A number of drug administration systems have been successfully utilized in recent times, however, there are still certain challenges that need to be addressed and advanced technology needs to be developed for successful delivery of drugs to their target sites. As a result, nanoscale drug delivery systems are currently under review to facilitate the Advanced Drug Delivery System.[7] Nanoparticles are specially designed and built systems that are measured in nanometers (nm). Generally, particle size is specially designed so that nanoparticle passes through the Fenestrations of the leaking cancerous Endothelium. Particle size also Determines whether circulating nanoparticles are operationalized and rapidly erased by the reticulo-endothelial (RES) system, that is mostly distributed in the liver, lungs, spleen and bone marrow. Unless the drug is administered in these tissues, the surface of nanoparticles should be altered to evade RES.[3] Pegylation is one such case, addition of polyethylene glycol to the surface of nanoparticles. This technology has been generating the "STEALTH" particle, that is invisible to macrophages. Another approach is to build particles with a hydrophilic surface to reduce opsonization, which slows down the clearance of macrophages. Hydrophilic polymers that cover the surface of nanoparticles repel plasma proteins and evade opsonization and clearance.[3] This was described as the effect of a "cloud". A variety of materials are used for building nanoparticles including ceramics, polymers, lipids and metals.Nanoparticle structures may contain primarily organic molecules or have inorganic elements that typically incorporate a metal as the nucleus. Nanoparticle structures have a variety of sizes and shapes, which include spheres, branched structures, shells, tubes, fullerene, emulsions and liposomes. Therapeutic medicines are incorporated into nanoparticles through entrapment, surface fixation or encapsulation. As a vehicle for drug delivery, nanoparticles can become biodegradable after drug targeting. Therefore, it is degraded and metabolized and does not accumulate and does not interfere with cell processes. This is important because high levels of non-biodegradable particles can result in a toxic side effect.[3]

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Types of nanoparticles in drug delivery:

Nanoparticles for medication administration are available in a wide range of shapes, sizes, and materials. The size and shape of each particle differ from each other with regard to the loading capacity of the medicinal product, the stability of the particles and the medicinal product, as well as the release rate and the administration efficiency of the drug.[3.] Nanoparticles are used as drug delivery systems because their sizes range from 3 to 200 nm.[4.]

Polymer-based drug carriers

The most common nanoparticle drug carriers are polymers. Polymers that are used in the polymer nanoparticle structure can be natural or synthesized.[5] Depending on the preparation process, the drug is physically trapped or covalently bound to the polymer matrix. Polymers such as albumin, chitosan and heparin are natural and have been an excellent material for the administration of oligonucleotides, DNA and proteins, as well as drugs. Recently, a formulation of paclitaxel nanoparticles, in which serum albumin is included as a carrier, has been implemented clinically for the treatment of metastatic breast cancer. Among man-made polymers like N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA), polystyrene-maleic anhydride copolymer, polyethylene glycol (PEG), and poly-L-glutamic acid (PGA). PGA was the first biodegradable polymer that was used in conjugated synthesis.[4]

Micelles

Micelles are spherical or globular structures which form when constituent molecules with a hydrophobic extremity cluster form the central nucleus of the sphere in a liquefied environment. The hydrophilic ends of the molecules are then brought into contact with the liquid medium surrounding the micelle structure and form a mantle.[3] Micelles are highly efficient in DDS due to their high capability, drug loading variable, high stability in physiologic conditions, lower dissolution rate, more drug accumulation in the targeted place, and surface modifications. Two polymeric micelles, known as NK911 and NK105, have been introduced onto the drug market and contain doxorubicin and paclitaxel, respectively.[5]

Dendrimers

They are 3D treelike structures regularly branched with a multifunctional core molecule. These dendrimers vary in size from 1.9 nm for G1 to 4.4 nm for G4.[1] These nanoparticles can support a variety of carrier, hydrophilic and hydrophobic molecules, and are useful administration agents for genes, medications and anti-cancer agents.[3] Polyamidoamine dendrimer, the most commonly used dendrimer in scaffolding, was conjugated with cisplatin. The easily changeable surface feature of dendrimers allows them to be conjugated simultaneously with several molecules such as imaging contrast agents, targeting ligands, or therapeutic drugs, yielding a dendrimer-based multifunctional drug delivery system.[4]

Liposomes

These structures are closed vesicles composed of lipid layers and are classified on the basis of the number of lipid bilayers as unilamellar or multilamellar.Unilamellar systems have an aqueous nucleus for encapsulating water-soluble medicines, while multilateral systems trap fat-soluble medicines.[3] At present, several types of cancer drugs have been applied to this system based on lipids among them liposomal formulations of the anthracyclines doxorubicin (Doxil, Myocet) and daunorubicin (DaunoXome) are approved for the treatment of metastatic breast cancer and AIDS-related Kaposi's sarcoma (22–24).In addition to the approved agents, many liposomal chemotherapeutics are currently undergoing clinical trials.[4]

Viral nanoparticles

A variety of viruses for example cowpea mosaic virus, cowpea chlorotic mottle virus, canine parvovirus, and Bacteriophages have been developed for biomedical and nanotechnology applications that include tissue targeting and drug delivery.[4]

Carbon nanotubes

Carbon nanotubes are carbon cylinders consisting of benzene cycles that have been applied to biology as sensors for the detection of DNA and proteins, diagnostic devices for the discrimination of various proteins from serum samples and vectors for the administration of vaccines or proteins. Antifungal drugs (amphotericin B) and anti-cancer drugs (methotrexate) have been covalently bound to carbon nanotubes with a fluorescent agent (FITC).[4]

Lipid nanoparticles

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Lipid emulsions have also been studied as a promising solution for administering drugs toaffected tissues. They have some advantages like good biocompatibility, biodegradability, physical stability and ease of large-scale production. Additionally, they may include hydrophilic, hydrophobic and amphipathic medications because of their structural character.[6] They have a size of less than 1 μm. They can function as carriers of drugs with very low solubility in aqueous environments. They can be released at a particular time and delivered to the target location by food, injections, etc.[5]

Tumor Targeting:

Treatment of cancer requires that the therapeutic agent specifically reach the tumor tissue at a precise concentration, after it has penetrated diverse biological barriers present in the body. Nanoparticles may be delivered to specific sites via size-dependent passive targeting or through active targeting so that the anticancer drug can selectively destroy cancer cells, avoiding healthy ones[9]. Drug particles are delivered efficiently to the target site by these two strategies. In passive targeting, diseased tissue such as a tumor takes advantage of a pathophysiological feature, while in active targeting, the drug carrier accumulates into the tumor region, then binds to the target cells using a targeting ligand, which leads to receptor-mediated internalization of nanoparticles within the cells.[10]

Passive drug targeting

The mechanism most frequently used to selectively deliver cancer treatments at the tumor site is passive targeting. The EPR effect allows carriers of nanoparticles to extravasate themselves from hyperpermeable tumor blood vessels and accumulate in tumor tissues. They accumulate more in tumors than in healthy tissues, releasing a greater quantity of their useful load specifically in the vicinity of cancer cells.[9]

Another factor contributing to passive targeting is the unique micro-environment around tumor cells, which differs from that of normal cells. Rapidly growing and hyper proliferating cancer cells have a high metabolic rate, and oxygen and nutrients are generally not sufficient to maintain this. Tumor cells use glycolysis to obtain additional energy, resulting in an acid environment.PH-sensitive liposomes are designed to be stable at a physiological pH of 7.4, but degraded to release an active drug into target tissues in which pH is inferior to physiological values, as in the acidic environment of tumor cells.[4]

Active drug targeting

Active targeting involves combining receptors with specific ligands, such as peptides or monoclonal antibodies, located on the surface of nanoparticles.[9] The nanocarriers will recognize the receptor and attach themselves to the target cells through ligand-receptor interactions, and the drug will be released inside the cell.[8] Some of the typically overexpressed receptors in cancer cells bind to folate, transferrin or galactosamine ligands. Therefore, by properly attaching the relevant fraction to the nanoparticle surface, active targeting can be achieved.[9]

Using the folate receptor example, where a folate-targeted conjugate binds to the folate receptor at the cell surface, the invasive plasmatic membrane envelops the receptor and ligand complex into an endosome. As the pH value inside the endosome becomes acidic and lysozyme is activated, the drug is released from the conjugate and enters the cytoplasm. The liberated drugs are then tampered with by their target organelles depending to the drug. In the meantime, the folate receptor released by the conjugate returns to the cell membrane to begin a second transport cycle by binding with novel conjugates targeted by folate.[4]

Targeted nanoparticles may also target tumors via triggered targeting, in which nanoparticles release their payloads in response to external stimuli, such as an electric or magnetic field, ultrasound, hyperthermia, or light.

Therapeutic and Diagnostic application of nanoparticles:

A variety of nanoparticle formulations for diagnostic and therapeutic applications have been developed recently as a result of recent advances in nanotechnology. The intrinsic properties of nanoparticles hold promise for integrating diagnostic and therapeutic agents into one nanoparticle formulation, allowing therapeutic applications, such as monitoring biodistribution and accumulation sites in the body, visualizing and quantifying drug release, and longitudinally assessing therapeutic outcomes. As a result, nanoparticle-based therapeutic treatments can be personalized by enabling patient selection and enhancing therapeutic efficacy. With their specific properties, nanoparticles may be incorporated into valuable therapeutic modalities. Their properties offer unique interactions with biomolecules both on

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the surface and inside the cells, enabling significant improvement in cancer diagnosis and treatment. There are about 20 clinically approved nanomedicines used for treatment. An example is Abraxane, an albumin bound form of paclitaxel with Cobalt of a mean particle size of approximately 130 nm that is used to treat breast cancer.[11]
More than 20% of therapeutic nanoparticles already in clinical or clinical evaluation have been developed for cancer treatment.

Nanoparticles for Medical Imaging

A crucial part of diagnosing and treating tumors is medical imaging. Nanoparticles such as iron oxide nanoparticles, which enhance imaging through optical, magnetic, acoustic, and structural properties, can serve a variety of purposes. A few studies have shown that introducing nanoparticles to target tissues can improve image contrast and provide better guidance during tumor surgery and diagnosis. For example, in cryosurgery, nanoparticles can facilitate the image detection of the ice balls quickly and accurately, which enables the treatment to become more effective.[12]

Nanoparticles for Cryosurgery

In addition to being low-invasive, low-cost, less traumatic, and less likely to cause postoperative complications, cryosurgery is also low-invasive and low-cost. Despite these advantages, however, there are still some drawbacks including insufficient freezing efficiency and freezing damage to surrounding tissues. AFP-1 has been used as a protective agent to improve cold ablation, but the effects are not perfect [72]. As nanotechnology developed, the concept of nano cryosurgery emerged. As a general rule, nano-cryosurgery involves introducing nanoparticles with a particular physical or chemical property into tumor tissues. Not only can nanoparticles be utilized toincrease freezing effectiveness and efficiency, but their properties can also be used to control the amount of ice ball formation and the direction. Nanoparticles freeze faster than conventional tissues and are more prone to heterogeneous nucleation, so nano-cryosurgery can simultaneously kill tumor tissue and spare surrounding healthy tissue from freezing. As shown by the results, nanoparticles can significantly speed up and facilitate ice formation in tissue under the same freezing conditions. Nanoparticles are able to kill tumor cells more effectively by increasing the speed and probability of ice formation in cells.[12]

Nanoparticles for PTT and PDT

In recent years, photothermal therapy (PTT) and photodynamic therapy (PDT) with nanoparticles have shown high efficacy, low invasion, and minimal side effects in treating tumors. As well as killing tumor cells directly, dead tumor cells can act as antigens and trigger a continuous immune response. Photothermal or photodynamic immunotherapy is the conversion of light energy into heat energy to kill cancer cells. Nanoparticles constructed using the PTT concept are a new type of light-to-heat conversion nanomaterial that can do just that. Nanoparticles offer many advantages for photothermal conversion compared to traditional materials. First, nanoparticles can effectively target tumors by aggregating the particles on their surface, thus increasing the tumor's ability to be enriched. Second, nanoparticles improve the performance of various imaging devices, such as CT, MRIs, and photoacoustic imaging, while traditional photothermal materials are less accurate.[12]

Nanoparticles for Radiotherapy

Radiation therapy (RT) consists of the use of rays to create ionizing radiation, which is an effective method of treating many primary and metastatic solid tumors. However, further improvements in RT's performance are still needed. As animaging guidance enhancement device, nanoparticles have demonstrated radio sensitizing properties, tumor-targeted delivery capabilities of radio sensitizing drugs, and radiation sensitizing properties in radiotherapy. Most nanoparticles at present are made from metals with high Z (atomic number) which have chemical inertness and strong radiation absorption capabilities after absorption of light. These metals can undergo several reactions, such as photoelectric effect and Compton effect, which can release a variety of particles such as optoelectronics, Compton electrons, and Auger electrons after absorption of light. Atoms in tumor cells generate free radicals when they react with organic molecules or water, leading to synergistic chemotherapy.According to their materials, chemotherapy-sensitized nanoparticles can be classified as special alloys, metals, or semiconductors. Special alloys include gold, silver, gadolinium, hafnium, platinum, bismuth, etc. Special alloys include titanium alloys. Among these, gold nanoparticles have become one of the most popular nanoparticles due to their high

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photoelectric absorption coefficient, good biocompatibility, and chemical stability.[12]

II. CONCLUSION AND FUTURE PERSPECTIVE:

Nanoparticles for cancer imaging and therapy have evolved rapidly during the last decade and it is expected that more and more will become clinical practice. Their controlled size and multifunctionality are the main reasons for their increasing applications as anticancer agents.[1]

In the future, nanoparticle technology and development for cancer chemotherapy delivery will continue to expand. The search for new tumor targets, novel ligands, new strategies for targeting, and particle stabilization will advance our ability to improve delivery at the tumor level while decreasing toxicity to normal tissues.[3] Nanoparticle drug delivery systems, unlike conventional therapeutics, have the advantage of being easily designed and tuned in order to reach the target site, not only to treat cancer but many other diseases still without an effective addition. The surface of the nanoparticles can be modified to improve their properties, increasing the retention time within the bloodstream by the incorporation of PEG, or targeting them selectively to tumor cells by active targeting with the coupling of an adequate ligand. More detailed knowledge is needed to interpret the routes of drug delivery to assist them in achieving the therapeutic level of the drug at the site ofaction.[9,10] A thorough study of the effect of PEG size and density on nanoparticle kinetics is needed. Furthermore, the clearance mechanism, metabolism, and excretion of nanoparticles and their components need to be studied more. Thus, further investigations in nanotechnology are necessary to develop formulations that can reach tumor tissues in sufficient concentrations, avoid uptake by the RES, and selectively kill cancer cells without harming healthy tissues.[3]

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