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NOVEL TARGETING APPROACHES OF NANOPARTICLES FOR ANTICANCER DRUG DELIVERY: A FOCUSED REVIEW

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ABSTRACT

Nanoparticles have presented a new paradigm in anticancer drug delivery to reduce adverse effects and improve therapeutic outcomes. Nanoparticle surface properties and morphology significantly affect the drug delivery to tumors while passive targeting. Conjugations with hyaluronic acid, transferrin and aptamers have shown to be effective in active targeting of anticancer drugs to tumor tissues. This review presents an overview of some credible techniques of passive and active drug delivery to tumors.

KEY WORDS: Nanoparticle, cancer, targeting, hyaluronic acid, transferrin, aptamer.

INTRODUCTION

Rigid nanoparticles are solid colloidal particles in size less than 1µm, in which the active principle (drug or biologically active material) is dissolved, entrapped, encapsulated and/or to which the active principle is adsorbed or conjugated to the surface.[1] Some scientists restrict the definition to structures with a size range of 1–100 nm in at least one dimension.[2] Two major types of particulate systems are used in nanomedicines, 1) drug molecules dispersed within a dense polymeric/lipid matrix, or 2) drug molecules dissolved in a liquid core or in a lipid or polymer micelles or vesicles. Various colloidal drug carrier systems like liposomes, niosomes and microemulsions which are similar to polymeric nanoparticles with respect to their shape, size and mode of administration, have been employed as an alternative to nanoparticles. However, the rigid nanoparticles offer additional advantages when compared to the other colloidal carriers, such as easier terminal sterilization, higher stability during storage and in-vivo, easy dispersion of lyophilized products for administration, protection of the drug against degradation due to encapsulation of the drug in the solid polymer matrix and modulation of the drug release profile by changing the polymer composition.[3,4,5]

Over the last decade, the biodegradable nanoparticles have gained enormous interest for cancer therapy. The polymeric biodegradable nanoparticles have been largely investigated for the purpose of controlled and/or targeted drug delivery. Biodegradable polymers are typically degraded into individual monomers, which are metabolized and removed from the body via normal metabolic pathways. A number of different polymers have been utilized in preparation of nanoparticles, but poly(lactide) (PLA) and poly(lactide-co-glycolide) (PLGA) have been the most popular ones.[6] PLA and PLGA are biocompatible and biodegradable and thus, they pose a minimal risk of toxic side effects in-vivo. The corona of the polymeric nanoparticle acts like a shielding layer to protect the encapsulated drug from plasma proteins in-vivo, while the targeting ligand facilitates the delivery of nanoparticles to the target site.

Nanoparticle size and shape

Since a number of anticancer drugs have a short half-life following administration due to their low molecular weights, hydrophobicity and degradability[7], it is important to study the effect of particle size and shape on the overall circulation time. Parenteral administration of the nanoparticles necessitates their size to be as small as possible in order to be able to reach the targeted destination especially since the inner diameter of the smallest capillaries in human body can be as minute as 4 µm.[8] Furthermore, the nanoparticles exhibit the "EPR (Enhanced Permeation and Retention) effect" due to the leaky tumor vasculature and poorly developed lymph system in tumors.[9] For the EPR effect to occur, it is desirable that nanoparticles be as small as possible. The lower limit for the nanoparticle size is set at 10 nm, to avoid the renal clearance, as the threshold diameter for the glomerular filtration is considered to be in the range of 8-10nm.[10]

A number of studies indicate that the nanoparticle shape could significantly affect their circulation time.[11] It was shown that the filamentous micelles as long as

18 µM could have a circulation half-life of almost twice that of the spherical particles.[12] It was reported that interaction of the nanoparticles with the macrophages and contact angle formed could be responsible for shape effect on the circulation time.[13]

Nanoparticle surface properties

Nanoparticles have high surface-to-volume ratios when compared to larger particles. Therefore, control of their surface properties is crucial to their in-vivo behavior. Intravenous administration of polymeric nanoparticles or conventional colloidal carriers, leads to their rapid removal from the blood circulation by the macrophages of the Mononuclear Phagocyte System (MPS), also known as Reticuloendothelial System (RES). Within seconds of introduction of nanoparticles in the bloodstream, plasma proteins called opsonins adsorb on the surface of nanoparticles and render them 'visible' to the macrophages, mainly the Kupffer cells or macrophages of the liver, which ultimately phagocytize them. Thus, the nanoparticles are removed from the bloodstream even before reaching their target site of action, making them totally ineffective.[14,15] There is no absolute method to completely inhibit this process of opsonization and phagocytosis of nanoparticles, but there are ways to slow it down.

Typically, it has been observed that plasma proteins are attracted more towards the hydrophobic surface as compared for hydrophilic surface. Also, research has shown a correlation between surface charge and opsonization, with the charged particles having higher chances of being opsonized than the neutral ones.[16] A widely used method to prevent opsonization is to shield the surface of nanoparticles by use of long hydrophilic polymer chains that can protect the charged and/or hydrophobic nanoparticles from being recognized by the plasma proteins. Examples of such polymers are: polysaccharides, polyacrylamide, poly(vinyl alcohol), poly(vinyl-2- pyrrolidone), PEG and PEG-containing copolymers. However, the most popular and commonly used polymer are PEG and PEG-containing copolymers and the method of decorating a particle surface by covalently grafting, entrapping or adsorbing PEG chains onto the surface is called PEGylation.[17]

Targeting tumor microenvironment

A major advantage of nanoparticles is their drug targeting potential, which has been widely studied in the field of cancer therapy.[18,19,20] Nanoparticles have the ability to passively target the chemotherapeutic drug to the tumor site by exploiting the tumor blood vessel characteristics. This ability to passively targeting of the drug could be due to the combination of EPR effect and passive diffusion. Additionally, the surface of nanoparticles can be conjugated to various targeting moieties such as antibodies, aptamers to achieve active targeting of the drug.

Passive Targeting: To satisfy the increased nutrition need of the multiplying tumor cells, there is rapid angiogenesis (formation of new blood vessels) in the tumor, which results in aberrant tortuosity and abnormalities in the basement membrane of newly formed tumor blood vessels. Thus, the incomplete tumor vasculature demonstrates porous blood vessels with gap size ranging from 100-700 nm depending on tumor type, allowing the entry of nanoparticles smaller than those gaps into the tumor interstitium. Moreover, the tumor lymphatic system is also poorly developed, resulting in fluid retention in tumors and high interstitial pressure at the center of tumors than at the periphery.[21] This causes the retention of the nanoparticles that gain entry into the tumor interstitium, since these particles are not readily extravasated into the lymphatic system. Hence, the combined phenomenon of entry into the tumor interstitium along with being entrapped in the tumor is termed as EPR effect. Therefore, many factors influence the EPR effect; 1) regional blood flow to the tumor, 2) permeability of the tumor vasculature, 3) structural barriers imposed by perivascular tumor cells and extracellular matrix, and 4) intratumoral pressure.[22]

Active Targeting: One of the major challenges in cancer chemotherapy today, is the targeted delivery of the therapeutic agent to the desired tumor growth site avoiding damage to the healthy organs. Active targeting involves peripheral conjugation of a targeting moiety, that will specifically bind to the tumor cells, to the surface of nanoparticles. Thus, the targeted nanoparticles, post intravenous administration, can reach the tumor site and selectively bind the tumor cells, leading to the reduction of chemotherapeutic side effects.

Following are some of the examples of the various ways in nanoparticles have been utilized to target drugs to cancer cells:

Hyaluronic Acid: Activated hyaluronic acid (HA) receptors CD44 and RHAMM are overexpressed on the tumor cells[23] and thus HA-anchored PLGA nanoparticulate carriers encapsulating doxorubicin were prepared which can bind to HA receptors and get internalized into the tumor cells, ultimately resulting in targeted drug delivery to the tumor cells. In this case, HA is linked to PLGA by a diamine PEG spacer and their targeted delivery would lead to increased exogenous concentrations of HA assumed to be involved in the inhibition of tumor metastasis. Thus, the HA-PEG-PLGA nanoparticles were able to deliver high concentrations of doxorubicin to the tumor as compared with monomethoxy (polyethylene glycol) (mPEG)-PLGA which reduced the tumor volume significantly after IV injection in the Ehrlich ascites tumor-bearing mice.[24]

Transferrin: Transferrin receptors (TfR) are overexpressed in tumor tissues as compared to the normal tissues and thus transferrin, a glycoprotein, can be utilized as a ligand for drug targeting to tumor.[25,26]

Conjugation of the amine group of Transferrin to the hydroxyl group of PLGA nanoparticles encapsulating the chemotherapeutic drug Paclitaxel, via the epoxy linker facilitates the transcytosis of the carrier system.[27] Transferrin has also been shown to overcome multi-drug resistance due to P-gp[28,29] which is overexpressed on the tumor cell membrane and known to limit the intracellular uptake of anticancer drugs thereby decreasing their therapeutic efficacy.[30] Thus, delivery of Transferrin conjugated paclitaxel loaded nanoparticles causes high and sustained intracellular drug levels as well as increase the antiproliferative action of the drug as compared to that of the unconjugated nanoparticles.

Aptamers: Farokhzad and Langer labs have successfully shown the delivery of aptamer conjugated polymeric nanoparticles to tumor cells for imaging as well as drug delivery purposes. They covalently linked a 5' amine terminated A10 RNA aptamer that binds to PSMA over expressed on the prostate tumor cells, to PLGA-PEG nanoparticles showing desirable size and drug loading. The conjugation was carried out using the carbodiimide chemistry in which the terminal carboxyl group of the polymer reacts with the 5' amine group of aptamer forming an amide linkage. These functionalized nanoparticles displayed active binding and cell uptake in-vitro as well as enhanced nanoparticle delivery to the prostate tumors in-vivo as compared to the equivalent non-functionalized nanoparticles. As reported in their study, the drug loaded nanoparticle-aptamer conjugate showed about 20% decrease in cell viability as compared to the drug nanoparticles alone. Whereas, the in vivo results obtained in mice, supported the in vitro results by confirming the superiority of nanoparticle-aptamer conjugate in targeting the tumor site.[31] Another study from the Farokhzad and Langer labs, have shown the use of PSMA targeted aptamer-nanoparticle conjugate to also deliver cisplatin to prostate cancer cells.

SUMMARY

Nanoparticles, owing to their characteristics and advantages, are being used extensively to study their potential in delivering various drugs/proteins. Their ability to show passive targeting as well as active targeting make them an attractive drug delivery approach especially in diseases like cancer where drug targeting is essential.

DISCLOSURE

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the paper. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this paper.

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