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Utilization of nanoparticulate therapy in cancer targeting

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Abstract: Cancer is a disease affecting millions of people worldwide. Early detection as well as appropriate treatment regimens are crucial in combating the deadly disease. The advent of nanotechnology has had a truly transformative impact on health care. Today, nanotechnology finds applications in multiple areas including diagnostics and therapeutics. The exponential growth in the field has made it possible to detect diseases such as cancer much earlier than previously possible. Additionally, nanoparticles are emerging as frontline candidates for the treatment of several types of cancer. Several clinical results suggest that nanoparticles possess the potential to reduce side effects and increase efficacy of treatment options, owing to some distinctive properties they display. This review provides a brief description of nanoparticle mediated tumor-targeting approaches with an emphasis on recent developments in the field.

Subjects: Pharmaceutical Engineering; Nanoscience & Nanotechnology; Nanobiotechnology

Keywords: drug delivery; nanotechnology; micelles; liposomes; cancer therapy; passive targeting; active targeting

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Eshwaran Narayanan received his Master's degree in Chemical Engineering from Arizona State University in 2015. His graduate research focused on the development of colorimetric plasmonic nanosensors for the detection of therapeutic levels of ionizing radiation for use in dosimetry. Broadly, his research interests include formulation development, radiation sensing, synergistic cancer treatments and nanotechnology. At present, he works as an R&D Scientist at Insys Development Company Inc., AZ, USA. His research here is focused on the development of sublingual/nasal spray products and oral solutions.

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PUBLIC INTEREST STATEMENT

This manuscript enables the target audience to focus on the salient features of nanoparticulate therapy that is being widely utilized in active and passive targeting, in today's nano age. This is extremely vital because the applications of these nanoparticles have wider ramifications in today's medical field, particularly in areas of cancer research, where these specially designed nanoparticles are engaged in an ever-lasting conquest of attempting to overcome some conventional disadvantages of standard chemotherapeutic regimens. This work attempts to make us realize the modern-day shift in trend toward targeted and nontargeted nanotherapeutics. We believe that this article will be appealing and informative to the journal subscribers as it adheres to the specific aims and scope of this journal and attempts to keep abreast with the current developments on this topic of interest.

1. Introduction

Today, nanoparticles find wide applications ranging from therapeutics and diagnostics to treatment monitoring and evaluation (Parveen, Misra, & Sahoo, 2012; Pushpavanam, Narayanan, & Chang et al., 2015; Pushpavanam, Narayanan, & Rege, 2016). Nanoscale materials exhibit distinctive properties that have made them attractive options in these fields. To cite some examples, the large surface area of nanoscale materials allows for its modification for better stability, biocompatibility and interaction with certain cells (Ambardekar, Wakaskar, & Sharma et al., 2013; Wakaskar, Bathena, & Tallapaka et al., 2015). In biomedical applications were transportation of the drug to the target site is critical, they offer solutions to long standing challenges such as nonspecific biodistribution and targeting, lack of water solubility, poor oral bioavailability and low therapeutic indices. Over the last two to three decades, nanotechnology has given rise to nanomedicine, a field with much promise and appeal (Wakaskar, 2017a).

Cancer is a disease affecting millions of people worldwide. For advanced-stage cancers in patients, treatment is often limited to chemotherapy or radiation. However, these treatment options come with their own set of drawbacks. With regard to chemotherapy, its toxicity and nonselective nature are major drawbacks. The administration of the drugs by itself could be challenging owing to its inherent characteristics. Chemotherapeutic drugs being nonspecific in nature result in significant damage to noncancerous tissues (Wakaskar, 2017e, 2017f). Additionally, majority of the chemotherapeutic drugs available in the market have a high pharmacokinetic volume of distribution and low molecular weight (Bharali, Khalil, & Gurbuz et al., 2009). The low molecular weights of these drugs make it susceptible to rapid excretion. Drug molecules that are circulating *in vivo* may be significantly bound to certain proteins or even lipids which are prevalent in plasma. This consideration is vital as it is a widely regarded phenomenon that only free drug molecules can display meaningful interactions with the target that can elicit the required therapeutic effect, for e.g., a particular receptor. Unfortunately, the jury is still out and there is a significant lack of scientific research to provide an in-depth outline of how these interactions contribute to the *in vivo* efficacy of either hydrophobic or hydrophilic drugs. Certain *in vitro* assays such as the shift assay have the ability to predict the concentration of the compound that is available to bring about the efficacy after specific interactions with the given target. These compounds which overcome the barrier of *in vitro* testing are then selected for advanced *in vivo testing*. A higher concentration of the drug is therefore necessary to achieve therapeutic benefits which at the same time makes toxicity inevitable. Another characteristic of these drugs which is not particularly favorable is its low therapeutic index. It is critical that the minimum effective concentration be reached for optimal treatment but unfortunately often these levels are exceeded. Together, all of these result in severe undesirable side effects such as nausea, emesis, bone marrow suppression, alopecia and the sloughing of the gut epithelial cells (Luo & Prestwich, 2002; Wakaskar, 2017g). Under these circumstances, tumor-targeted delivery of chemotherapeutic drugs is perhaps one of the most important steps for chemotherapy. Naturally, there is great interest in the development of nanodelivery systems for cancer therapeutics. By using nanotechnology in drug development and delivery, researchers are attempting to drive nanomedicine to be able to deliver the drug to the targeted tissue, release the drug at a controlled rate, be an effective and reliable drug delivery system and circumvent clearance by bodily processes. An ideal system would facilitate specific targeting thereby enhancing the efficacy while minimizing undesired side effects.

In developing a safe and effective drug carrier that selectively delivers cytotoxic drugs to tumor cells, two strategies are popular. The first approach commonly referred to as “passive targeting” relies on fundamental differences in the structural features of solid tumors (Wakaskar, 2017b). These differences lead to somewhat selective extravasation and retention of long circulating nanocarriers. In the other approach, the surface of the nanocarriers is modified to specifically recognize tumor cells. The governing principle in this case is specific interaction between ligands such as nucleic acids, antibodies, etc. on the carrier surface and receptors expressed in tumor

environments. This approach is referred to as "active targeting." The objective of this article is to review these tumor-targeting strategies with an emphasis on recent developments.

2. Passive targeting

Tumor cells are known to exhibit pathophysiological characteristics different from that of regular cells. Passive targeting capitalizes on these differences to target delivery of the drug to the site of interest through what is commonly referred to as the enhanced permeability and retention (EPR) effect (Parveen et al., 2012). EPR is a phenomenon where molecules of certain sizes accumulate to a greater extent in tumor cells than normal cells. The accumulation is attributed to differences such as hypervasculature, lack of effective lymphatic drainage and increased production of permeability mediators (Maeda, Wu, & Sawa et al., 2000; Wakaskar, 2017c). Maeda et al. reported one of the first tumor targeted delivery of anticancer styrene-maleic acid copolymer-conjugated neocarzinostatin in 1979 (Maeda, Takeshita, & Kanamaru, 1979), eventually leading to the introduction of the phenomena of EPR in solid tumors in 1986 (Matsumura & Maeda, 1986). For a better understanding, we refer the audience to an excellent review by Maeda et al. describing the pathophysiological mechanisms of the EPR effect, anatomical differences of tumor blood vessel, various factors involved and artificial augmentation of EPR effect with respect to tumor-selective delivery, and the advantages and problems of macromolecular drugs (Maeda, Bharate, & Daruwalla, 2009; Wakaskar, 2017h). The discovery of EPR has proved to be a breakthrough in tumor-targeted drug delivery (Greish, 2007; Gullotti & Yeo, 2009; Maeda, 2001; Matsumura & Maeda, 1986) and has been exploited for delivering various therapeutics by researchers. Despite the potential that nanocarriers offer as therapeutic agents through EPR, it is critical to select those with apposite properties so as to enhance the period of circulation and prevent immune response. Toward this end, researchers have found that nanocarriers with a size range of 10–100 nm is ideal (Wakaskar, 2015). This is because the kidneys filter out particles smaller than 10 nm and the liver can capture particles greater than 100 nm in size (Alexis, Pridgen, & Molnar et al., 2008; Caliceti & Veronese, 2003). Another important consideration is the charge of the nanocarrier; neutral or anionic carriers are optimal and escape renal elimination (Guasch, Deen, & Myers, 1993; Rennke, Cotran, & Venkatachalam, 1975). Oftentimes, the nanocarriers are also surface coated to evade opsonization and phagocytosis by the reticuloendothelial system (Wakaskar, 2017i). A common surface coating utilized is polyethylene glycol (PEG) which is believed to reduce the protein interactions on the surface of the nanocarriers, preventing their binding to opsonins (Oku, Tokudome, & Asai et al., 2000; Owens & Peppas, 2006; Wakaskar, 2017j). Also, this coating of PEG significantly imparts an *in vivo* stealth nature to the nanoparticles by reducing the inter-particulate attractive forces and thus rendering effective repulsive forces to incoming blood components such as plasma proteins. In effect, this reduces clearance of these nanoparticles from the body. Significant increase in antitumor potency of doxorubicin through a similar mechanism has previously been reported (Colbern, Hiller, & Musterer et al., 1999). Doxil/Caelyx, a pegylated liposomal doxorubicin formulation, demonstrated prolonged circulation time and unique toxicity profile. Unlike free doxorubicin, its toxicity profile was characterized by minimal alopecia, mild myelosuprresion and no apparent cardiac toxicity. For a brief review on the preclinical toxicology of Doxil, the reader is referred to the work by Working and Dayan (1996). Doxil was found to be up to six times more effective than free doxorubicin (Gabizon, 2001; Gabizon, Shmeeda, & Zalipsky, 2006) and was approved for the treatment of advanced ovarian cancer, metastatic breast cancer and AIDS-related Kaposi's sarcoma (Peer, Karp, & Hong et al., 2007). Chemically modified heparins which possess non-anticoagulant activity have recently been recognized to effectively inhibit angiogenesis, metastasis and tumor growth due to their interference with growth factors (Jayson & Gallagher, 1997; Soker, Goldstaub, & Svahn et al., 1994). They have garnered significant attention as safe drug carriers since they do not induce hemorrhage. Similar to other macromolecules, these drug-containing amphiphiles passively target tumors by the EPR effect. On this front, in an attempt to develop an effective anticancer drug delivery system, Park et al. prepared doxorubicin-loaded heparin nanoparticles (Park, Lee, & Kim et al., 2006). The doxorubicin-loaded heparin nanoparticles displayed sustained release patterns and an *in vivo* study showed that doxorubicin-loaded heparin nanoparticles induced tumor volume reductions of 74%. These results suggest that the drug-loaded

heparin nanoparticles might provide a novel therapy for squamous cell carcinoma and human umbilical vascular endothelial cell proliferation. Heparin has multifold applications not only in squamous cell carcinoma but also in other cancer types such as lung carcinoma, breast and pelvic cancer, to name a few (Von Tempelhoff, Harenberg, Niemann, & Hommel et al., 2000). Specifically, low-molecular-weight heparin such as nadroparin or certoparin is effective against venous thromboembolism and may thus prolong survival in highly malignant cases of advanced cancer progression (Klerk, Smorenburg, & Otten et al., 2005; Von Tempelhoff et al., 2000). In another study, Cho et al. proposed a new anticancer drug conjugate system for *in vivo* tumor targeting and inhibition of angiogenesis (Cho, Moon, & Park et al., 2008). This system uses sodium deoxycholate-heparin nanoparticles to target tumors based on the principle of EPR and chemical conjugation. These nanoparticles showed greater antitumor effects as well as a significant decrease in endothelial tubular formation, providing new insights into the design of bioconjugates for targeted drug delivery. Chytil et al. also exploited the EPR effect for targeting solid tumors (Chytil, Etrych, & Koňák et al., 2008). Briefly, various conjugates of doxorubicin covalently bound by hydrazone bond to the drug carrier based on N-(2-hydroxypropyl)methacrylamide copolymers were synthesized. Drug conjugation with polymers is advantageous since it could potentially reduce toxicity, enhance bioavailability, eliminate undesirable body interactions, prolong blood clearance, and improve solubility and stability. The hydrazone bond facilitates pH-sensitive linkage of the drug to the polymeric carrier and allows for drug release in endosomes/lysosomes in tumor cells following a pH change (from pH 7.4, the pH of blood to pH 5–6, the pH of endosomes) (Mrkvan, Sirova, & Etrych et al., 2005; Rodrigues, Roth, & Fiebig et al., 2006; Ulbrich & Šubr, 2004). Treatment of mice bearing EL-4 T-cell lymphoma with the above conjugates via intravenous injection resulted in enhanced tumor accumulation and significant tumor regression with up to 100% of long-term survivors.

Kim et al. reported on the tumor-targeting ability of cisplatin-loaded glycol chitosan nanoparticles based on the EPR effect as well (Kim, Kim, & Park et al., 2008). It was observed that the nanoparticles accumulated in the tumor sites in tumor-bearing mice. The nanoparticles released the drug in a sustained manner for a week, showed higher antitumor efficacy and was less cytotoxic than free cisplatin. More recently, considering the complexity involved in fabrication procedures of nanocarriers reported, Akao et al. developed a lipid complex by using poly(γ-glutamic acid), a cationic lipid, and doxorubicin which demonstrated significant antitumor activity (Akao, Kimura, & Hirofuji et al., 2010). The complex was able to encapsulate over 90% of the drug and effectively accumulated in solid tumors based on the EPR effect. The complex may possess several unique advantages, including simplicity of nanoparticle preparation, high drug-carrying capacity, appropriate size to allow deeper penetration based on EPR effect into solid tumors and lack of necessity to modify the chemical structure of the drugs. Data from sarcoma 180–bearing mice indicated that the complex could be potentially useful in cancer chemotherapy.

Although EPR facilitates accumulation of nanocarriers, there remains a potential for improvement with regard to targeting, given some limitations to this approach. First, targeting relies on the degree of tumor vascularization and angiogenesis (Allen & Cullis, 2004; Wakaskar, 2017k). Thus, the effect may not be realized in all tumors owing to differences in porosity and pore size of the blood vessels (Bae, 2009; Hobbs, Monsky, & Yuan et al., 1998). Second, elevation of interstitial fluid pressure which is witnessed in tumor tissues hinders the penetration of therapeutic agents (Netti, Hamberg, & Babich et al., 1999). For the interested user, a review article by Nehoff et al. discusses the factors giving rise to this phenomenon (Maeda et al., 1979). Third, tissue penetration is a significant barrier to the efficacy of a nanomedicine. The presence of extracellular matrix and dense population of cells around blood vessels limits the ability of nanomedicines to penetrate. As a result, the anticancer efficacy of the nanocarriers is often impaired. Furthermore, PEGylation itself can be a hindrance since it not only prevents the interaction between nanocarriers and opsonins but also between the nanocarriers and cell surface (Gryparis, Hatziapostolou, & Papadimitriou et al., 2007; Hong, Huang, & Tseng et al., 1999; Kaasgaard, Mouritsen, & Jørgensen, 2001; Mishra, Webster, & Davis, 2004; Romberg, Hennink, & Storm, 2008). Fourth, heterogeneity of tumor blood flow interferes with the homogeneous distribution of a drug within

the tumor (Jain, 1988). Therefore, in order to improve upon EPR, researchers have come up with several strategies such as altering physiologic conditions, physiological modifications of tumor vasculature, inducing morphological changes in perivascular cells, etc. (Kobayashi, Watanabe, & Choyke, 2014). Detailed discussion on these is beyond the scope of this article as several articles on each of these topics are available.

3. Active targeting

The main concept behind active targeting is that the target substrate recognizes the ligand attached to the nanoparticles making their foray to the tumor sites. These representative ligands may consist of peptides, nucleic acids, sugars and antibodies (Saha, Vasanthakumar, & Bende et al., 2010). Usually, the target sites may consist of molecules such as proteins, nucleic acids or sugar molecules which are present on the surface of cells. The functionalization of nanoparticulate matter with surface-attached ligands depends on several factors such as ligand density, ligand to polymeric material ratio as well as the end-group chemistry of the ligands in effect along with the polymeric matter. The two important attributes that govern the efficiency of any active targeting system consist of targeting specificity and delivery capacity of the payload in this ligand functionalized nanoparticulate system. The specificity, in turn, is regulated by the way of interaction of this system with the nonmalignant cells, which also reveals the toxicity potential of this system. Biodistribution of these surface-functionalized nanoparticles in various organs also governs the extent of specificity of these nanoparticulate systems. One other important feature of active targeting is that these targeted nanoparticles must be in proximity of their target antigen to recognize and attach to it (Florence, 2012). There are various challenges associated with the delivery of these actively targeted nanoparticles. Their concentration in the blood varies because of the systemic clearance, and this process affects the amount of these nanoparticles reaching and exhibiting their effect on the tumor cells. It is always preferable to have these actively targeted nanoparticles exhibiting prolonged blood circulation times. Active targeting cannot significantly alter the extent of distribution of nanoparticles, and hence, modifications that improve upon the blood circulation times of these nanoparticles are favorable in achieving an optimal nanodelivery system.

Active targeting also aids in increasing the extent of internalization of these nanodelivery systems into the target cells, thus also improving upon the efficacy of the drugs loaded or attached to these delivery systems (Bertrand, Wu, & Xu et al., 2014). Anti-HER2 immunoliposomes internalize and selectively bind to Human Epidermal Growth Factor Receptor-2 (HER-2) overexpressing cancer cells. As a result, it has been noted that anti-HER2 targeting ligands greatly increase the affinity of these liposomes toward cancer cells, thus providing a vehicle potentially for intracellular drug delivery (Kirpotin, Drummond, & Shao et al., 2006).

Nontargeted liposomes are generally taken up by the macrophages, which in effect reduce their uptake into the targeted site of cancer cells, thus reducing the efficacy of the targeted nanoparticulate system (Kirpotin et al., 2006). Intracellular transport of these targeted as well as nontargeted nanoparticles is a complex phenomenon which can be affected by several intricate processes such as receptor-mediated internalization. These actively targeted nanoparticles are known to overcome several issues regarding internalization by exhibiting sufficient endosomal escape and protecting the cargo from these endosomal sequestrations. Considerable *in vitro* and *in vivo* work has been validated to establish the successful fundamental concepts of active targeting. The best example is that of ligands, which are targeted to folic acid internally by complexing with Epidermal Growth Factor Receptors (EGFR) antibodies and have been known to improve internalization quite successfully into malignant cells (Low, Henne, & Doorneweerd, 2007). Ligand density plays a crucial role in determining successful conjugation of these nanoparticles to the respective ligands. Optimal stoichiometric ratio of the ligand to the nanoparticle has to be determined for successful conjugation as well as appropriate internalization of these nanoparticles into the cancerous cells (Wakaskar, 2017d). Moreover, the stability as well as the integrity of these

nanoparticles must be maintained even after successfully conjugating the targeting ligand to the surface of the nanoparticle. In several preferred cases, covalent attachment of the ligand to the nanoparticle is performed; however, physical adsorption of these targeting complexes has also been used with a great measure of success. If appropriate end-functional groups are present on the nanoparticulate surface, then targeting is relatively facile and can be carried out in a single step. For example, surface treatment functionalization of gold surfaces can be performed by utilization of end thiol groups, whereas other nanoparticulate materials need the introduction of amino or hydroxyl functional groups to promote the targeting reaction (Ghosh, Han, & De et al., 2008; Liong, Lu, & Kovochich et al., 2008). As these strategies are utilized to take advantage of the phenomenon of nanoparticulate binding to cell surface receptor, various examples have been studied in the literature that study their distinct advantages over their nontargeted counterparts.

4. Conclusion

Although there are several instances of nanoparticulate therapy in cancer, there are various concerning areas too. As the size of the nanoparticles is increased due to large cargos and provision of multiple points of attachment for targeting ligands, it begins to act as a deterrent for tumor penetration and its overall efficacy, if not carefully optimized. Further substantiating mechanistic evidence is required to understand the exact mechanism of tumor penetration in targeted over nontargeted nanotherapeutics to subsequently enhance the accumulation of drug in the tumor cells. In this area of research, there are growing concerns over nanoparticulate toxicity, as the complexity of the nanoparticles is enhanced due to their engineered surfaces and provision of multiple targeting ligands. Thus, the size and surface properties of these nanoparticles ultimately govern their *in vivo* behavior and more experimental evidence is required to facilitate further understanding of their efficacy and overall biodistribution. Undoubtedly, nanoparticulate therapy with its increased surface functionality and optimization of the targeting ligand ratio will be a preferred mode of drug delivery in the future due to the various advantages elicited. Better methodologies will be discovered to understand the overall mechanism of targeted as well as nontargeted nanotherapy and preferential choices will be executed over the mode of delivery, taking into consideration the nature of the payload and type of tumor. Although myriad challenges exist for these modes of delivery, their potential advantages should lead a successful foray of their development and thus facilitate the continuing emergence of targeted as well as nontargeted nanoparticulate technology.

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