Review Article

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SURFACE MODIFIED RECEPTOR MEDIATED DELIVERY SYSTEMS FOR SITE SPECIFIC TREATMENT OF CANCER

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ABSTRACT
The treatment of the cancer has many challenges now a days due to side effects of the treatment. However, in the modern formulation development the concept of the site specific drug delivery for disease treatment in the body is considering as continuous challenges. Observing the challenges in convectional technique site specific drug delivery system has good potential to reduce adverse side effects, efficiently improve the human body health with very low toxicity. This review article elaborates the current challenges and prospective of surface modified drug carrier systems for delivery of protein for site-specific treatment of cancer and anti-cancer drug.

INTRODUCTION

The concept of a drug carrier with targeted specificity has captivated scientists for many years, and successful efforts have been made in the last decade to achieve this goal [1]. The ultimate form of targeted drug delivery system should be a realisation of Paul Ehrlich's "magic bullet concept," which documents drug delivery to a preselected targeted cell type exclusively [2].

Liposomes have recently gained prominence among all targeted drug delivery systems due to their biological inertness, lack of antigenic, pyrogenic, or allergic reactions, and increased stability. Liposomes are colloidal or microparticulate carriers that develop spontaneously when such lipids are hydrated in aqueous media [3]. Liposomes are made of biocompatible and biodegradable materials and are made up of aqueous volume trapped by one or more bilayers of natural or synthetic lipids. Highly lipophilic drugs with a partition coefficient greater than 5 are almost entirely entrapped in the lipid bilayer of liposomes.

Antineoplastic agents used to treat lung cancer, solid tumors, testicular cancer, breast cancer, many forms of leukaemia, lymphoma, and other cancers have been linked to a variety of serious side effects, including bone marrow depression, which induces granulocytopenia, agranulocytosis, throbocytopenia, and aplastic anaemia, lymphocytopenia, and suppression of lymphocyte function.

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Chemotherapy for cancer is often associated with harmful side effects. Cancer could be treated without side effects if an anticancer drug could only deliver the right dose at the right time to the right place. Since liposomes are basically non-toxic and biodegradable, their size, materials, and modifications with different molecules are easily regulated, and they can deliver large amounts of either hydrophilic or hydrophobic agents, liposomal formulation is thought to be useful for such delivery method.

Liposome delivery to the right place is always a work in progress. Active and passive targeting are also taken into consideration for this reason. Conventional liposomes, on the other hand, are often stuck by the reticuloendothelial system [RES] in organs like the liver and spleen before reaching their intended destination. On the other hand, since the vasculature in tumor tissues is leaky enough to extravasate liposomes and circulating liposomes can accumulate passively in tumor tissues, passive targeting, especially targeting to tumor tissues, could be achieved by reducing RES trapping. Liposomes containing lipid derivatives of PEG or saturated phospholipids such as DSPC with cholesterol have rendered targeted liposomal therapy more feasible by decreasing RES uptake and thereby prolonging circulation period [4].

PEG is particularly useful due to its ease of preparation, low cost, molecular weight controllability, and ability to bind to lipids or proteins, including antibodies, using a variety of methods. PEG inhibits serum protein binding, i.e. opsonins, which mark the liposome for macrophage clearance. Antibodies should be bound to the distal end of PEG chains that are already attached to the liposome membrane, according to our hypothesis. In order to prepare long circulating [RES avoiding] liposomes, we have chosen several functionalized PEG derivatives such as DPPE-PEG-Mal and DSPE-PEG.

The most common approach for actively targeting liposomes to tumor cells is to bind ligands to the liposomal surface, allowing for a precise interaction with the tumor cells. Antibodies or antibody fragments, vitamins, glycoproteins, peptides [RGD-sequences], and oligonucleotide aptamers have all been used as ligands for this function. Immunoliposomes, which use an antibody or antibody fragment as a targeting ligand and a lipid vesicle as a carrier for both hydrophilic and hydrophobic drugs, are a fascinating prospect in cancer therapy among the various

active targeting approaches. The transport phase, in which immunoliposomes migrate from the site of administration [often i.v. administration] to the target cells, and the effector phase, which involves precise binding of immunoliposomes to target cells and subsequent delivery of entrapped drugs, are the two stages of targeted drug delivery with immunoliposomes.

Immunoliposomes for tumor treatment must meet a set of criteria aimed at maximising the targeting effect of immunoliposomes provided systemically in the bloodstream. The antigen binding site of the liposome-conjugated antibody must be accessible in order for the antibody to associate with antigen on the surface of target cells without being disrupted. In contrast to the rate of extravasation in the tumor, immunoliposome blood clearance must be reduced. The immunooliposome must be able to effectively load and maintain a particular anticancer drug. Finally, drug and antibody integration must be safe enough to allow liposomal entry into tumor tissue while neither of these agents is lost.

In the proposed work, an attempt is made to establish long circulating [RES avoiding] immunoliposomes for site specific delivery of selected anticancer drugs by adding functionalized PEG derivatives over the liposome membrane and attaching a suitable monoclonal antibody to the distal end of the PEG chain. Compared to traditional liposomes, long circulating immunoliposomes have the following advantages.

1. Decreased RES uptake and prolonged circulation time
2. Selective active targeting to tumor tissues
3. Increased efficacy and therapeutic index
4. Reduction in toxicity of encapsulated agent

The creation of hybridoma technology, which enables a large quantity of monoclonal antibodies to a wide variety of cell determinants to be generated, has aided the use of an antibody molecule as a homing device. The monoclonal antibody 21B2 or MN-14, which is specific for the human carcinoembryonic antigen [CEA], was chosen for this study to see whether immunoliposomes injected intravenously would extravasate into solid tumor tissue and bind to tumor cells. We've also chosen CEA positive human gastric cancer strain MKN-45, as well as other CEA positive human solid tumor strains [Endocervical adenocarcinoma, epithelial ovarian cancer, and etc]. Again, instead of using the entire antibody, the current study is attempting to use the Fab' fragment, which reduces the

immunogenic effect of the Fc part and improves RES clearance through precise recognition by phagocytic cells carrying Fc receptors. Via specific thiol groups in the hinge region, Fab' fragments also allow for better conjugation to liposomes containing DPPE-PEG-Mal.

SURFACE MODIFICATION OF NANOFORMULATIONS

Surface alteration of nanoparticles changes their surface properties and improves the delivery system's performance in biological environments. Covalent bond formation between the functional groups on the surface and the ligands is typically used to conjugate the nanocarrier's surface with a particular ligand [5].

Surface alteration techniques include electrostatic adsorption and surface coating. The existence of various functional groups on the surface of albumin nanoparticles, such as carboxylic and amino groups, offers various possibilities for surface modification of dependent delivery systems. The following are ligands that are used for a variety of purposes ranging from pharmacokinetic modulation to drug release modification and targeting:

Surfactants

Surfactants are used in formulation to adjust the pharmacokinetic parameters. Modifications with Polysorbate 80, for example, effectively decreased doxorubicin's multiple toxicities, such as respiratory, testicular, and haematological toxicity [6][7].

PEG

PEGylation of delivery systems is done to reduce their immunogenicity and extend their circulation half-life, thus increasing nanoparticles' passive tumor targeting capability [8].

Cationic polymers

Cationic polymers are mostly used to delay the release of drugs. The only way to secure nanoparticles from enzymatic degradation is to coat them with biocompatible materials, which eliminates the use of dangerous crosslinkers for nanoparticle stabilisation, such as glutaraldehyde crosslinking, which is used to stabilise albumin and gelatin nanoparticles prepared through desolvation or coacervation. Surface coating of anionic albumin nanoparticles with cationic polymers such as polyethylenimine [PEI] can regulate the rate of drug release and is dependent on the concentrations of PEI used for coating [9].

Thermosensitive polymers

Shen et al. developed new thermal targeting drug carriers by carbodiimide [EDC] coupling the thermo-responsive poly [N-isopropylacrylamide-coacrylamide]-block-polyallylamine [PNIPAM-AAm-b-PAA] to the carboxylic group on the surface of albumin nanospheres, and successful targeting was observed with these nanoparticles [10].

Folic acid

Folic acid receptors are one of the many receptors that are overexpressed in cancer cells. Folic acid is a vitamin with a low molecular weight. Folic acid has many advantages as a targeting agent, including its stability, low cost, non-immunogenic nature, compatibility with organic solvents used during processing, and the fact that it is the primary substrate for folate receptors; it binds to folate receptors at cell surfaces with high affinity and is internalised through receptor mediated endocytosis [11]. The carboxylic group of folic acid was conjugated to the amino groups on the surface of albumin nanoparticles using the carbodiimide [EDC] coupling technique [12].

Monoclonal antibodies [mAbs]

mAbs are an interesting group of ligands that have emerged for tumor targeting. Many cancers, including breast, ovarian [13], colorectal, non-small cell lung, head, neck, and prostate cancers, as well as glioma, have surface overexpression of the epidermal growth factor receptor [EGFR]. EGFR-2 [HER2] is used as a tumor targeting marker in the treatment of patients with metastatic breast cancer [14]. Trastuzumab [Herceptin®], a humanised anti-HER2 specific antibody, was used to modify the surface of the nanoparticles by forming an avidin–biotin complex between the biotin-binding protein [NeutrAvidin] attached to the nanoparticles and the biotinylated antibody for Human serum albumin [HSA] nanoparticle. In HER2-overexpressing cells [cell lines BT474, MCF7, and SK-BR-3], Wartlick et al. conjugated HSA nanoparticles with trastuzumab and evaluated them in HER2-overexpressing cells [cell lines BT474, MCF7, and SK-BR-3] and found that successful internalisation of the nanoparticles through receptor-mediated endocytosis is time and dose dependent [15].

Peptides and proteins

In the literature, Expression of high levels of αvβ3 integrin [a membrane receptor for extracellular matrix ligands such as vitronectin and fibronectin] have been found in cancer cells from

different entities [16]. The cyclic arginine–glycine–aspartic acid [RGD] peptide ligand has a high binding affinity for the αvβ3 integrin [17]. Dubey et al. prepared RGD peptide-anchored sterically stabilised BSA nanospheres [RGD-SN] containing 5-fluorouracil for targeting tumor vasculature, and found that RGD-SN is significantly more efficient than free fluorouracil in preventing lung metastasis, angiogenesis, and effective tumor regression [18].

Preclinical and Clinical Investigations of Nanoparticles

Albumin-paclitaxel nanoparticles made with novel nab technology have a diameter of 130 nm and were approved for the treatment of metastatic breast cancer in 2005. In a phase I review, the toxicity profile, pharmacokinetics, and mean therapeutic dose [MTD] of nab-paclitaxel were investigated [19]. Nineteen patients with advanced solid tumors obtained doses ranging from 135 to 375 mg/m² as an infusion without any premedication. There was just minor hematologic toxicity. At the maximum dose tested [375 mg/m²], two patients developed grade 3 superficial keratopathy. 300 mg/m² was determined to be the MTD. Ibrahim et al. came to the conclusion that nab-paclitaxel can be provided quickly and safely without the need for premedication. 63 women with metastatic breast cancer received 300 mg/m² nab-paclitaxel by intravenous infusion without premedication in a multicenter phase II trial [20]. Despite the lack of premedication, no serious hypersensitivity reactions were identified in the phase II analysis. Routine ophthalmological tests showed no serious ocular events like superficial keratopathy, indicating that this toxicity occurred by chance in the phase I sample or only occurs at doses higher than the MTD. 210 Chinese patients with metastatic breast cancer were enrolled in an open-label multicenter phase III trial. In contrast to solvent-based paclitaxel, preliminary findings indicated that nab-paclitaxel offers higher response rates and a longer time to tumor progression without increased toxicity [21].

In a variety of human tumor xenograft models, nab-paclitaxel has outperformed paclitaxel in terms of antitumor efficacy. At the MTDs, however, mice treated with nab-paclitaxel showed a substantial improvement in antitumor response. Data on nab-antitumor paclitaxel's response and tumor uptake were comparable to albumin-binding prodrugs like DOXO-EMCH. The change of the MTD of nab-paclitaxel and DOXO-EMCH over the respective free drug in mice resulted in an average increase in drug tumor accumulation of 3 to 6 fold at an equitoxic

comparison. At an equitoxic contrast, there is a 3 to 6 fold rise in drug tumor accumulation. The pathophysiology of tumor tissue is defined by angiogenesis, hypervasculature, and impaired lymphatic drainage, and it mediates the enhanced absorption of albumin-based drug delivery systems in solid tumors. Transcytosis induced by albumin binding to a cell's 60-kDa glycoprotein receptor, as well as albumin binding to SPARC [secreted protein acid and rich in cysteine], increases nab-paclitaxel accumulation in tumor cells [22]. Abraxane was tested for adjuvant, neoadjuvant, and first-line treatment of breast cancer, as well as other indications such as non-small cell lung cancer, ovarian cancer, and pancreas cancer, after receiving FDA approval. Other nab-technology-based products in clinical trials include those containing docetaxel, rapamycin, and other drugs.

Transferrin protein was coupled to various nanoparticles to achieve targeted delivery to cancerous cells. When doxorubicin-loaded apotransferrin nanoparticles were administered intraperitoneally, they transmitted the drug more effectively against cell-mediated ascetic liver cancer than free doxorubicin. Hepatocytes take up transferrin-bound iron through receptor-mediated endocytosis into a low-density vesicle compartment, which is followed by iron release and transferrin recycling. However, it has been stated that transferrin receptor-1, transmembrane protein divalent metal transporter 1 [DMT1], and divalent metal transporter ZIP14 are all involved in transferrin-mediated iron transport.

Gelatin-based nanoparticles were used to deliver pDNA encoding VEGF receptor-1 in the body [23][24]. Gelatin [Gel], thiolated gelatin [SHGel], and polyethylene glycol-modified gelatin [PEG-Gel], as well as polyethylene glycol-modified thiolated gelatin, were used to encapsulate pDNA [PEG-SHGel]. Several anticancer genes can be delivered by a variety of gelatin-based delivery systems, according to in vivo studies. Following intravenous administration of and PEG-SHGel nanoparticles, approximately 13-15% of the recovered dose accumulated in the tumor for up to 12 hours, according to a gelatin-based delivery method. Overall, PEG-Gel nanoparticles [25]can provide a safe and effective method for delivering therapeutic plasmid to solid tumors. In addition, in vivo studies showed that cationic gelatin microspheres containing NK4 pDNA inhibited angiogenesis in Lewis lung carcinoma tumors and suppressed disseminated pancreatic cancer cells.

Epidermal Growth Factor Receptor Targeting in Cancer

The epidermal growth factor receptors [EGFR]/Her1/ErbB1 are cell-surface receptors that belong to the ErbB family of tyrosine kinases. Because of their abnormal expression in many epithelial tumors and their effect on growth and survival in malignant states, they have gained a lot of attention for molecular targeting of cancer therapeutics [26]. Many therapeutic agents have been developed as a result of advances in genetic engineering and understanding of the EGFR signaling pathways in cancer, including monoclonal antibodies [mAbs], small molecule tyrosine kinase inhibitors [TKIs], antisense oligonucleotides, antibody dependent immuno-conjugates, and other agents such as FR-18, peptides, affibodies, nanobodies, and others [27] [28].

By blocking the ligand-binding region, mAbs bind to the extracellular domain of EGFR and compete with endogenous ligands to inhibit ligand-induced EGFR tyrosine kinase activation[29] [30]. The two most advanced mAbs that target the extracellular domain of the EGFR are cetuximab and panitumumab. Cetuximab [Erbitux] is a chimeric [mouse/ human] monoclonal antibody for intravenous infusion that was approved by the United States Food and Drug Administration [USFDA] in February 2004 for the treatment of metastatic colorectal and head/neck cancer [31]. Panitumumab [Vectibix], on the other hand, is a completely human mAb specific to EGFR that was approved by the USFDA in September 2006 for metastatic colorectal cancer. Panitumumab was the first monoclonal antibody [mAb] to show that KRAS [Kristen RAS] can be used as a predictive biomarker, and it was approved by the European Medicines Agency in 2007 and Health Canada in 2008 for the treatment of refractory EGFR-expressing metastatic colorectal cancer in patients with wild-type KRAS. In July 2009, the US Food and Drug Administration approved Erbitux for the treatment of KRAS wild form [non-mutated] colon cancer.

CONCLUSION

The research on receptor-mediated nanocarriers is currently very active, progressing from studies on non-therapeutic targets to studies on therapeutic targets. More research on these systems against multiple receptors, as well as hybrid therapies with receptor-mediated nanocarriers, have recently been released. However, we still have a long way to go, especially in terms of understanding receptors, which is crucial for receptor-mediated delivery. The primary advantage of receptor-mediated nanocarriers over passive nanocarriers may be their ability to accumulate within tumors for longer periods of time due to their binding to and/or absorption by cancer cells, preventing rapid redistribution into the systemic circulation. Ongoing research on different forms of drug delivery systems based on receptor mediation are discussed, as well as the potential and challenges, and a future study pattern is introduced.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Shiroya Milankumar Nathabhai and Fenil Vanpariya designed the work and made necessary corrections and revisions in the manuscript. Miteshkumar Malaviya collected the content and performed the literature review and also contributed to drafting the manuscript. All the authors framed the final manuscript.

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