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Targeting Tumour Blood Vessels with a Liposomal Drug Delivery system for Cancer Treatment

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Abstract

By providing various drug delivery methods and controlled-release distribution tactics, nanotechnology provides an alternative to traditional treatment alternatives. Due to their high biodegradability and general lack of toxicity, liposomes provide a flexible platform for a number of various delivery strategies that may improve the distribution and targeting of medicines to tumours. Due to fenestrated blood arteries within tumours, liposomes spontaneously enter tumours, causing recognised increased permeability and associated medication retention effects. Liposomes are appealing carriers for molecular imaging applications because they can be utilised to transport radioactive moieties, such as radiotracers, which can be bound at various points inside liposomes. Using the phage display method, various high-affinity and selectivity peptides can be delivered to various targets. In this study, covalent peptide-PEG-PE anchors were used to link gelatinase-binding peptides discovered by phage display to liposomes, resulting in a tailored drug delivery vehicle. A good approach for tumour targeting is to use gelatinases as extracellular targets. Based on our research, focused drug delivery outperforms non-targeted drug delivery in terms of effectiveness.

Keywords: Liposome; Transparent tumor; Blood vessels; Nanotechnology; Anti-cancer agents; Targeted drug delivery

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Introduction

Cancers continue to cause major clinical and social concerns as a widespread, commonly occurring disease. The main challenge facing the world is lowering cancer mortality, and research into cancer treatment is becoming more and more popular. The rising prevalence of the most common malignancies in low- and middle-income nations continues to be a significant concern despite the advancements made in cancer therapy. More importantly, despite the approval of numerous new anticancer medications for tumour prevention or therapy, the overall cancer mortality rate has not significantly dropped from previous decades. Sadly, the often used chemotherapeutics are also associated with serious side effects. Numerous efforts have been undertaken to create brand-new, extremely effective tumor-targeting medications. However, the traditional cytotoxic medications continue to be the first choice for patients because of the frequent occurrence of resistance concurrent with targeted therapies as well as the higher budgets of targeted drugs, which account for the restricted utilisation in clinical settings. In order to prevent and treat cancer, it is still necessary to create anticancer medications that are more potent and less hazardous [1].

Delivering enough medication to tumours while causing the least amount of harm to healthy tissues is one of the main objectives of an effective cancer treatment programme, the majority of chemotherapy drugs cytotoxically invade normal human tissues without discrimination and do not preferentially accumulate at tumour sites. The dose that reaches the tumour can occasionally be as low as 5% to 10% of the doses that build up in healthy organs. The fact that interstitial fluid pressure (IFP) in solid tumours is higher than in normal tissues prevents transcapillary transfer of chemotherapeutic medicines or antibodies, which is one cause for the failure of medications to accumulate at target

sites. The anticancer effect is lessened and the damaging effect on healthy cells is boosted in this approach. The amount of anticancer medication that can be administered to a patient is frequently constrained out of concern for doing serious harm to them. These less-than-optimal doses cause insufficient responses from the tumour, which results in disease relapse and treatment resistance. As a result, the reason why the majority of cancer medications fail in clinical trials is not because they lack the ability to kill cancer cells, but rather because they are unable to be given at doses high enough to completely remove the tumour without severely injuring the patient [2].

In order to increase the ability of anticancer drugs to more precisely target tumours and avoid healthy tissues, several strategies have been devised. Encapsulating medications in particles that deliver them preferentially to tumour locations is one of the most efficient tactics. For instance, it has been discovered that liposome particles can transport radionuclides, genes, and chemotherapeutic drugs to tumour locations. Encapsulating anticancer medications in liposomes coupled with moieties, such as antibodies and peptides, that target particular types of target tumour cells or tumour vasculatures is another potential approach. It is conceivable to transport chemotherapy medications contained within liposomes conjugated with such moieties to the cytosol by receptor-mediated endocytosis by using internalising ligands for targeting. This article highlights the most recent work on creating liposomal drug delivery systems that target blood arteries in solid tumours using peptide ligands. The use of both targeting and non-targeting liposomes to encapsulate and deliver chemotherapy medications to tumour areas are discussed, as well as the finding of peptides that can target tumour blood arteries [3].

Liposomal nanotechnology offers a flexible platform for investigating a number of strategies that might improve the transport and targeting of medicines to malignancies. Liposomes can be used as drug carriers in drug delivery systems because they are a biodegradable and largely harmless platform that can be used to encapsulate both hydrophilic and hydrophobic molecules (DDSs). Liposomes are appealing carriers for molecular imaging applications because they can be utilised to transport radioactive moieties like radiotracers, which can be bound at various points inside liposomes. In this study, liposomes were combined with gelatinase-binding peptides to create a specific drug delivery system [4].

Intraliposomal encapsulation of various targeting agents or therapies can be done in one of three ways: I to the lipid bilayer, which can bind hydrophobic conjugates; (ii) to hydrated compartments for water-soluble components; (iii) by covalent binding directly or by using spacer to the outer lipid leaflet, depending on the active targeting or drug delivery application. Given that the reticuloendothelial system (RES) captures most traditional liposomes that are not protected by polyethylene glycol chains (PEGs) or any similar steric water transporting material, delivery of these nanoformulations to the RES is easily accomplished. By changing the particle surface chemistry and charge, such as by coating the surface of the liposomes with positively charged lipids, physiologically active proteins, or sugars, it is possible to improve the uptake of RES. By altering the liposomal surface, long-circulating liposomes have been created for the goal of agent distribution to target organs other than the RES. The assessment of drug bioavailability requires knowledge of the in vivo biodistribution and targeting kinetics of liposome-encapsulated medicines [5].

Methods and Materials

Without exception, all chemicals were purchased from Sigma-Aldrich (St. Louis, Missouri, USA), and culture media were from Gibco Life Technologies (Paisley, Scotland). PEG-PE-NHS and all the other lipids utilised in this investigation were provided by Avanti Polar Lipids Inc. (Alabama, USA).

Using Fmoc-chemistry, peptides were produced on an Applied Biosystems 433A automated synthesiser (Foster City, CA, USA). Peptides were dissolved at a concentration of 1 mg/ml in 0.05 M ammonium acetate (pH 8), and then combined with H2O2 for 40 min at room temperature, adding 0.5 ml of 3% H2O2 for every 100 mg of peptide. Reversed phase HPLC was used to purify the peptides, and mass spectrometry analysis was used to determine their molecular weight [6].

In aqueous solution, monomers of CTT2-PEG3400-DSPE (i.e.CTT2-PEG-lipid) spontaneously formed micelles with a diameter of about 14 nm (i.e.CTT2-micelles), the hydrophobic core of which was formed by DSPE lipid chains, and the hydrophilic surface being created by PEGylated CTT2-peptide. To track the time-varying tissue distributions and tumour uptakes of CTT2-micelles, radioiodine I-125 (125I, half-life = 13 hrs.) was covalently tagged onto the particles. 90% radiochemical purity was attained [7].

Using the IODOGEN system, all liposomal formulations and peptides were radiolabeled with iodine-125 (125I) (Pierce, Rockford, IL). Using iodogen as a catalyst, the CTT2-PEG3400-DSPE peptide was tagged with 125I. A tube containing 10 g of dried iodogen and 100 g of CTT2-PEG3400-DSPE peptide construct was added 5 MBq of Na125I (Amersham, Buckinghamshire, England) in 0.5 ml PBS. The elution from PD-10 columns was used to purify the 125I-bound particle fractions. In a gamma counter, the peptide's activity was assessed (Cobra II, Packard Instruments) [8].

Discussion

Although traditional approaches that focus on finding alterations in the transcriptome or proteome in cancer have many advantages, a lot of emphasis has been paid to substantial changes in function, such as regulating ROS level, which may be a successful anticancer strategy. Undoubtedly, a variety of clinical chemotherapeutic medications, including doxorubicin, daunorubicin, and epirubicin, can kill cancer cells by boosting ROS generation. However, the indiscriminate cytotoxicity, unpleasant reactions, and chemo resistance that comes with the usage of these medications. A novel approach to treating cancer may involve repurposing medications with proven safety profiles that are created by reducing ROS creation or enhancing ROS production. Repurposed medications' lack of cancer-specificity, nevertheless, may be a problem. Furthermore, ROS are viewed as having two opposing effects in cancer. The multidirectional molecular activity of ROS results in numerous uncertainty. The

creation of repurposed medications for ROS still needs to address a few major problems[9].

Increasing the selectivity of ROS-related medicines that have been repurposed as therapeutic medications is another significant hurdle. ROS-responsive photodynamic therapy can achieve good outcomes because cancer cells thrive on levels of ROS that are somewhat higher than those in their normal counterparts. To date, new ROS-responsive prodrugs, probes, theranostic prodrugs, and nanotheranostics that enable the monitoring of ROS with temporal and geographic precision and enable the selective death of tumour cells have been produced. In fact, commercially used platinum-based medications have been successfully modified using ROS-responsive prodrug methods, demonstrating improved therapeutic efficacy and decreased adverse effects. Therefore, the creation of drug-inspired ROS-responsive groups, probes, and nanoparticles would significantly enhance the selective treatment of cancer [10].

Conclusion

The main objective of current oncology research is the creation of highly selective anticancer medications that can distinguish between tumour cells and normal cells. It is quite likely that medications contained in ligand-conjugated liposomes will be used to target tumour cells and the vascular system. To accurately deliver chemotherapeutic drugs to tumour cells or blood arteries, peptides that specifically bind to tumour targets can be linked to the PEG terminal of sterically stabilised liposomes. A new class of chemotherapeutic delivery devices with superior pharmacokinetics, regulated biodistribution, efficacy, and safety profiles are peptide-mediated liposomes that target the vasculature.

Conflict of Interest

None

Acknowledgement

None

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