

Dendrimers as Emerging Nanotherapeutics In Cancer Phototherapy

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Abstract

Phototherapy, which includes photodynamic therapy (PDT) and photothermal therapy (PTT), is a promising non-invasive treatment of cancers because of its highly located tumor specificities and minimal adverse reactions on normal tissues. Phototherapy alone, however, frequently causes reappearance of tumors that mainly prevents their clinical applications. Phototherapy involves light irradiation of target tissue. Numerous molecular photosensitization devices and photosensitive nanocarriers are developed with the aim of increasing selectivity and power. Usually, effective targeting entails harnessing the interaction between cell surface receptor and a ligand for better tissue aggregation.

1. Introduction

Phototherapy on cancer treatment has drawn growing interest in cancer treatment because of its high efficiency, usability, minimal trauma to normal tissue and high tumor selectivity. Basically two main types of phototherapy include photodynamic therapy (PDT) and Phototherapeutics [1,2]. Precisely, PDT is phototoxic therapy of different wavelengths of light triggered to produce singlet oxygen as well as various reactive oxygen species (ROS), which induce toxic radiation. PDT is a phototoxic therapy which includes photosensitizers. PTT uses photothermal substances for light absorption and transformation into heat at the tumor site by thermally

ablazing or hyperthermic killing of cancer cells. Phototherapy alone, however, can not kill cancer cells completely because of distribution, unequal heat and hypoxicity within the tumor [3]. Laser irradiation of the target includes phototherapies for cancer [4,5]. Using ultraviolet (UV) light for lupus diagnosis, Niels Ryberg Finsen received Nobel Prize in 2002 [6]. Phototherapy shows efficacy to treat many diseases including cancer [7]. When used in superficial conditions, it is minimally invasive and relatively safe.

Improved photosensitizer phototherapy can be categorized into two classes i.e. phototherapy (PTT) and photodynamic therapy (PDT). Both the methods are used to activate photosensitive molecules using fixed light wavelengths to produce therapeutic effects. The theranostic systems in nanomaterials have an excellent potential for phototherapy. To order to achieve synergistic effects, phototherapy can be used as a stand-alone or in conjunction with traditional chemotherapy [8]. Three components needed to PDT are light source, oxygen, and photosensitizer (PS). When irradiated, the PS receives a photon and converts it into an excited state. In type I reactions, the PS reacts directly to radicals with substrates, while in type II reactions, O_2 reacts with PS to generate reactive singlet oxygen. It is suspected that Type II reactions are more important to PDT. Singlet oxygen affects only the immediate environment in which it was created, usually within a radius of 20 nm. The delivery of a PS to particular target is therefore capable of identifying the site of therapeutic efficacy [9].

2. Nanomaterials for phototherapies of cancer

In the field of multifunctional nanoparticular synthesis, significant progress was made over the past few years, with outstanding outcomes in cancer treatment [10-12]. Latest theranostic nanocarriers are magnetic and gold nanoparticles, polymeric nanoparticles, micelles, liposomes, dendrimers and carbon nanomaterials.

Dendrimers, a flexible class of polymer nanoparticles for nanomedicine, are innovative forms of materials that have gained growing popularity over the last few years. These spherical 3-dimensional hyper-branched molecules are composed of multifunctional cores and branches. The most commonly used and researched dendrimers, which have been synthesized to date are polyamidoamine (PAMAM), poly(propylene imine) (PPI), Polyester and Carbosilane dendrimers [13].

3. Targeting mechanisms of dendrimers

3.1 Passive targeting

Trapping and accumulation of nanocarriers in tumors by changing size and surface characteristics is generally termed as passive targeting [14]. The differences between the tumor and the normal physiological tissue are based on this. The microenvironment of tumor and enhanced permeation and retention (EPR) are two main factors influencing passive targeting. Cancer cells show an elevated anaerobic metabolic rate and an acidic micro-environmental upregulation of glycolysis. Tumor cells also use other specific proteins, such as matrix metalloproteinases, to produce metastases. In contrast, the interstitial stress of angiogenesis, new blood vessel formation, and reduced lymphatic drainage at the center of tumors are certain tumor tissue characteristics. Such features cause nanoparticles to aggregate selectively and maintain interstitial tumors, resulting in the EPR effect. Nanoparticles must measure between 10 nm and 200 nm to prevent leakage into blood capillaries, which will make it small enough to prevent capture of macrophages in the reticuloendothelial system. Particularly essential for passive targeting are certain inherent features of nanocarrier [15]. PEGylation of nanoparticle or other molecules that increase half-life of a nanoparticle, by coating or linking of polyethylene glycol (PEG) chains has shown that PEG-modified liposome and micelle have improved passive targeting effects in tumors and increased blood circulation clearances in tumor-bearing mice, which contribute to active PDT operation [16]. The EPR-based passive targeting is simple and *in vivo* active targeting system still has a range of limitations. Some tumors may not show the EPR effect, particularly in the early stages. In fact, the permeability of the blood vessel in the EPR impact dependent nanoparticle can be reduced in effectiveness, even in one single tumor. Active targeting and physical force systems that can be triggered are built to address these drawbacks, in order to attain additional proficient targeting.

3.2 Active targeting

The persistent need of food for tumor cells to proliferate triggers the over-expression of different receptors. Active targeting is targeted at nanomaterial receptors in the tumor that are affinity to these over-expressed receptors. The effective targeting is distinguished by its ability for better tumor selection and aggregation typically through receptor-mediated endocytosis in contrast to

passive targeting. Specific ligands such as nucleic acids, proteins, and peptides take part in effective targeting on the basis of the ligands attraction for particular surface receptors of the cell. While PEGylation improves nanoparticle half-life, PEG numbers should be carefully chosen for effective targeting methods, because the abundance of PEG can prevent the ligand-recipient interaction. In order to circumvent this, the target ligand is attached at the end of the PEG group. However, large ligands such as proteins generally mitigate the obstacle from PEG and increase the life of the nanocarrier [17]. A recent study of the effects of carriers on ligands on the effective absorption found that the absorption of nanoparticles is directly linked to the amount of surface ligands [18]. Higher surface transfer nanoparticles strengthened binding which could lead to more efficient active guided delivery systems due to increased ligand-receptor interactions. Objectives may typically be categorized as proteins and peptides, nuclear acids and other ligands of the receptors. They can be divided into various groups in this situation.

The structures of nanocarriers to produce a desired therapeutic effect are based on two fundamental principles i.e. passive and active receptor targeting. They should reach the target site with limited intensity or volume loss during their distribution in the body. In addition, they should selectively target and destroy the target cells with a controlled release system without damaging the underlying healthy tissue. Based on numerous targeting methods, nanoparticles appear to be able to follow these requirements [19].

4. Dendrimers for cancer drug delivery

The dendritic nanosized carrier system has shown promising chemotherapeutic treatments and functions as a diagnostic tool due to the new generation of nanoparticles. Dendrimers are being used for various other applications including bone targeting as represented (Fig. 1). Dendrimers consist of properties involving monodispersibility, surface modification, and higher volume of internal pores, which make this nanocarrier suitable for targeted drug delivery [20,21]. The key features of dendrimer-based nanocarriers are to act as drug delivery vehicles for the higher uptake of anticancer agents in cancer cells. In addition to this, it increases the solubility, increases the drug retention time in the systemic circulation, and also facilitates passive targeting via EPR and active targeting by surface modification [21,22].

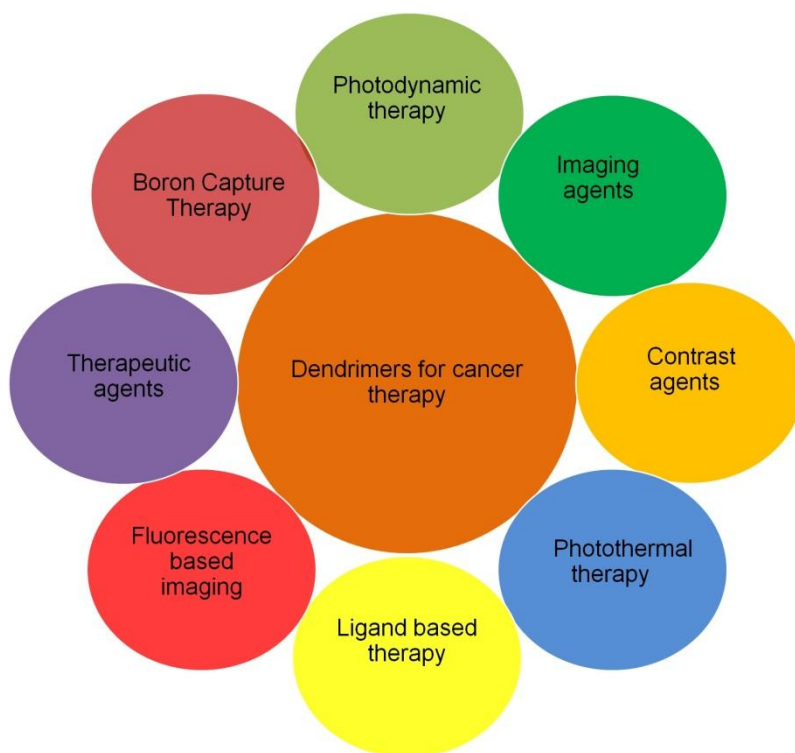


Fig 1. Various applications of dendrimer-based nanocarriers in cancer therapy

The EPR mechanism acts as increased anticancer macromolecule permeability inside the tumor vasculature and as a lower efflux rate from the cancer cells [23]. The PAMAM dendrimers conjugate with folic acid loaded with methotrexate of particle size <5 nm; these conjugated dendrimers consisting of particles <50 nm exhibiting higher cellular uptake of drugs in cancerous cells shown by confocal microscopy are ideal for EPR effect. Advances in therapeutic nanomedicine lead to the development of dendrimeric nanocarriers as diagnostic agents in magnetic resonance imaging (MRI) and act as a contrasting agent in boron neutron capture therap. Dendrimers have huge potential in the delivery of nucleic acids, proteins, and peptides by forming dendrimer-antibody conjugates utilized for in vitro diagnosis during cancer screening of biomolecules [24-26].

5. Types of dendrimers used for cancer therapy

5.1 PAMAM-PEG dendrimers

The cationic polymers such as PAMAM are reported to be toxic and unsuitable for the clinical use. To solve this problem, a group of scientists have prepared neutral polymers for dendrimer synthesis and reduced the cationic charged associated toxicities by surface functional group

alteration of PAMAM with polyethylene glycol (PEG). A PAMAM-PEG conjugated dendrimer came to existence that shields cationic charge. This can be entrapped with chemotherapeutic agents and delivery to the targeted sites can be achieved [27-29].

5.2 Glycodendrimers

These carbohydrate-derived macromolecular dendrimers consists of carbohydrate-oriented receptor affinity that leads to a novel drug delivery and diagnostic approach. Glycodendrimers are a monodispersed and macromolecular system where carbohydrate ligands are oriented at the surface of dendrimers. N-acetyl glucosamine anchored dendrimer was reported to present wide application in cancer therapy by inducing immunomodulation response [30,31].

5.3 Poly L-lysine dendrimers

Poly-L-lysine (PLL) dendrimers are synthesized where this amino acid was introduced with the intention to decrease the toxicity related to polymeric charges on the surface of nanocarriers. PLL dendrimers are reported for the entrapment of doxorubicin and its delivery with folate receptor targeting ligand. An in vitro drug release study performed under tumor mimicking acidic pH environment exhibited antiangiogenic effects for anticancer agents. This PLL dendrimer has shown fascinating properties that include biocompatibility, biodegradability, and acceptability for clinical purpose [32,33].

5.4 Triazine dendrimers

This is a special structural dendrimer that demonstrates the capacity to model multifunctions. The central synthesis of the dendrimers is provided with diammonium butane, diamine ethylene, ammonia and citric acid. Three conjectures at the core of the dendrimer consist of triazine dendrimers. Such dendrimers consist of a cage framework that can hold molecules for foreign visitors. Lim et al. thoroughly examined the impact of tissue distribution and tumor permeation of such dendrimers in cancer therapy on the volume of and amount of PEG chains. Authors also observed the molecular dynamics and antitumor behavior of paclitaxel-laden triazine dendrimers [34-36].

5.6 Carbosilane dendrimers

The CeSi bonded branched moiety with optimum energy and low polarity is known as carbosilane dendrimer. The polarity of these dendrimers can be altered by the surface modification of the peripheral chemical groups and can be converted into hydrophilic structure.

The core of this dendrimer is generally synthesized by 1, 3, 5-trihydroxybenzene core. This causes less steric hindrance in functional groups than dendrimers with a silicon atom core. It had shown prominent applications in nucleic acid delivery in AIDS without viral vector [37,38].

5.7 Phosphorus dendrimers

These are phosphorous atoms containing dendrimeric nanocarriers that are highly biocompatible and widely utilized in biomedical engineering research. Enormous applicability of this type of dendrimer is due to the phosphorus atom, which is an important element present in living organism biomolecules. The positive response of these dendrimers has been seen on the growth of nerve cells and cytotoxic T-cells. It is also useful in delivery of biological imaging agents and development of biosensors. Due to the amphiphilic nature of this carrier it can easily permeate through biological barriers. These metallodendrimers have high potential against antineoplastic cells and they seemed to operate through different mechanisms as compared to native metallodrugs, therefore they are opening new doors for improving cancer therapy [39].

5.8 Poly(amidoamine-Organosilicon) dendrimers

The poly(amidoamine-organosilicon) (PAMAMOS) dendrimers consist of internal hydrophilic polyamidoamine (PAMAM) on interior and interactive lipophilic organosilicone on outer surfaces. They are inverted unimolecular micelles possessing excellent combined properties such as hydrophilicity as well as lipophilicity. PAMAMOS dendrimeric network occupied into self-supportive elastomeric and elastomeric film coatings. The properties of this film depend on the generation of the PAMAMOS dendrimers [40-42].

6. Dendrimers in cancer phototherapy

A fluorescent target ligand, which was insisted on tumor penetration peptide iRGD (CRGDKGPDC) and ICG derivative cyprine, was covalently combined with PAMAM dendrimer for the preparation and maintenance of the fluorescence and heat capacity of the single dendrimer density theranostic nanoplateform iRGD-cyprine PAMAM-DTX (RCPD) which could generate enhanced singlet oxygen species [3]. In addition, in vitro and in vivo clinical trials have shown that, relative with phototherapy or chemotherapy alone, the combined chemophototherapy of RCPD with NIR light treatment will appreciably improve anticancer effectiveness and decrease the chance of reappearance of cancer. The multifunctional nanoplastic iRGD-cyprine-PAMAM-DTX (RCPD) enhanced phototherapy and chemical therapy in a synergic

way with improved cancer treatment capabilities. In particular, the cypate first reacted by amidation to iRGD, then iRGD-cypate reacted with PAMAM via amide reactions to form RCP dendrimers. The synthesized RCPD process is shown in Fig. 2. The docitaxel (DTX) was finally embedded in the inner core of RCP dendrimers [43].

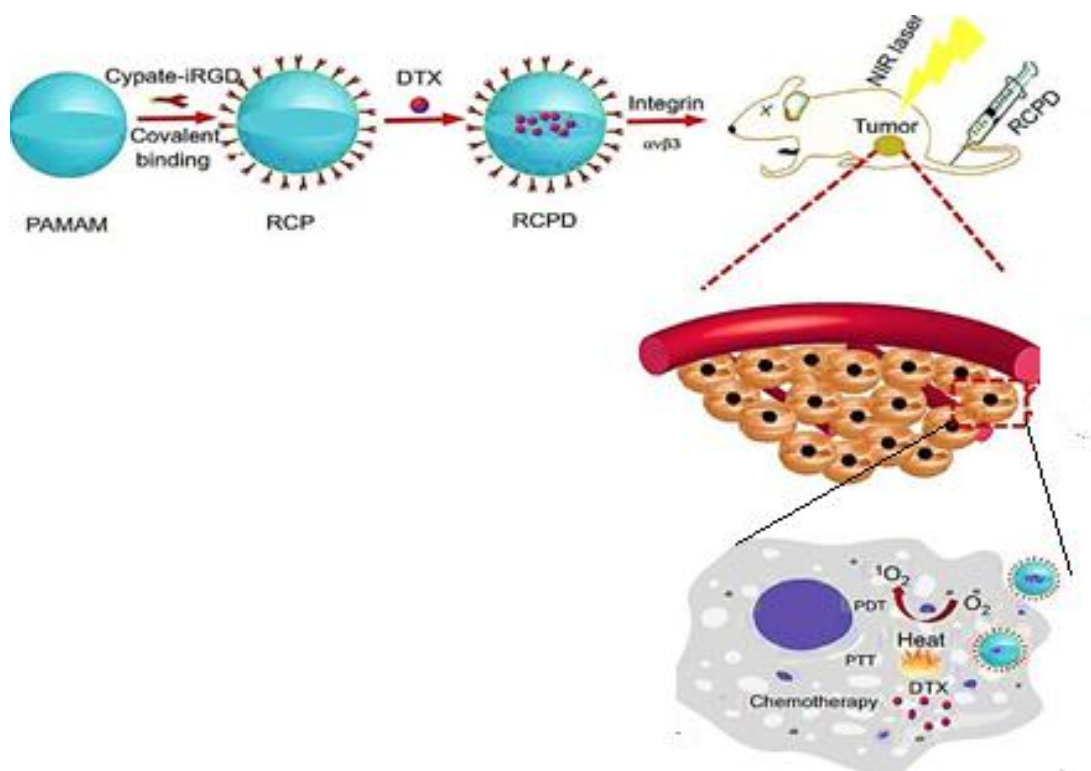


Fig.2: Schematic description of the integrated chemophoto treatment of cancer cells in the theranostic system [43]

7. Conclusion

Dendrimers have become an outstanding solution to the application of chemotherapeutic agents and can be used for diagnostic purposes. The dendrimeric systems can be modified to achieve the targeting objective in accordance with the microenvironmental conditions of the tumor. PEGylation, which also increases blood circulation speed, may resolve the cytotoxicity and hemolytic toxicity of cationic dendrimers. A cancer-specific hybrid chemotherapy can be accomplished by modulation of dendrimeric processes for active and passive tumor cell absorption, penetration and preservation.

8. References

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