Dendrimer Applications for Cancer Therapies

Xintao Yan¹,a,†, Yefei Yang²,b,†, and Yuchen Sun³,c,†

¹Queen Mary University of London Engineering School, Northwestern Polytechnical University, Xian, Shaanxi, 710000, People's Republic of China
²Queen Mary University of London Engineering School, Northwestern Polytechnical University, Xian, Shaanxi, 710000, People's Republic of China
³Queen Mary University of London Engineering School, Northwestern Polytechnical University, Xian, Shaanxi, 710000, People's Republic of China

arorschach.t62@mail.nwpu.edu.cn, btonyyang2061@mail.nwpu.edu.cn, csunyc@mail.nwpu.edu.cn.

†These authors contributed equally.

Abstract. Human cancer therapy is a major issue in modern medical science. Lots of emerging materials are developing rapidly. Dendrimers, as a nanocarrier, are now widely used in the field of biomedicine, pharmacy, and so on. As a super-branched macromolecule, dendrimers have a series of outstanding properties. Such as simple to functionalize, have nano & symmetric dimension and cavities for host-guest entrapment. It has made much progress in drug and gene delivery. Dendrimers have higher efficiency by perfecting the surface modification methods. The small molecules, DNAs, therapeutic agents, and more can be loaded into dendrimers. Also, the cytotoxicity is reducing gradually. This review aims to make a summary of dendrimers' history and provide guidance for future research. This review gives a brief review of dendrimers' properties, presents how dendrimers developed in drug and gene delivery, what drawbacks are remaining to resolve.

1. Introduction

Nowadays, people are paying more and more attention to health issues. Cancer, which is considered one of the most serious health issues, has aroused people's concerns. However, due to the complex medication environment and methods, those chemics for cancer therapy that ought to satisfy the stringent requirements for solubility, stability, and bioavailability are urgently needed. Dendrimer, a type of highly ordered and branched polymeric molecules, just happened to satisfy such demands, especially in the process of gene delivery and drug delivery for cancer therapy [1].

Human beings have fought against cancer for thousands of years since it was firstly recorded in ancient Egypt in 2500 BC. Nowadays, there are about 1,000,000 people die of cancer every year. As a result, people worldwide are trying to explore ways to fight cancer to prevent it from taking more lives. Although gene therapy and drug therapy can potentially treat cancer, the clinical implication is not effective because of the lack of an efficient delivery system [2].

Dendrimer was originally created as a wonder molecule of chemistry in 1978 [3]. The application of dendrimers as medical chemicals started in the late 1990s [1]. After decades of development and innovation, various dendrimers' applications in cancer therapy have been verified by thousands of experiments and put into clinical application. They have well-defined and uniform sizes and shapes [4].
Their special architecture that can be highly controlled makes them apply to work as systems for drug and gene delivery applications [5-6]. The internal cavities of dendrimers can encapsulate the drugs and oligonucleotides for cancer therapy. Besides, those drugs and oligonucleotides can bond to the surfaces of dendrimers through electrostatic or hydrophobic interactions or react with the functional groups to form a covalent bond [7-8].

This essay aims to give a brief review of the application of dendrimers in cancer therapy, including several parts, beginning with the history and structure of dendrimers and their properties, especially those that have been used in clinical medicine. It then focuses on the specific application of dendrimers in gene delivery and drug delivery for cancer therapy. Subsequently, it evaluates the advantages and disadvantages of applying dendrimers in cancer therapy dialectically and concludes about the feasibility and sustainability of its development prospects.

2. Dendrimer Structure and Properties

Dendrimers were firstly synthesized in 1984 by D. A. Tomalia and his colleagues [9]. The name dendrimer is originated from the ancient Greek word *dendron* and *meros*, which means trees and part [10]. The branched tree-like architecture is the most significant feature of this class of macromolecules. Dendrimers have symmetric, highly branched structures, leads to an obvious difference between classical monomers and oligomers [9].

Dendrimers consist of three parts: a central core, inner branches, and exterior surface (or end groups). Figure 1 shows the general structure of dendrimers for pharmaceutical applications [11]. The central core influences shape and production. Inner branches radially connected to the central core; generation (G) number determines the molecule's radius. The Exterior surface is modified with functional groups. The drugs can be loaded in many ways, i.e., encapsulated, conjugated on the surface, and conjugated into the cavity.

![Figure 1. Structure of pharmaceutical dendrimers](image)

The generation (G) number of dendrimers means the number of branching layers. With the G number increasing, the molecular mass of dendrimers increasing exponentially.

Dendrimers can be synthesized by two main methods: divergent and convergent.

a) The divergent method is a two-step process. (I) exhaustive Michael addition to a suitable amine initiator core with methyl acrylate and (II) exhaustive amidation of the resulting esters with large excesses of ethylenediamine [16]. Step II demonstrates a disadvantage of the divergent method, the excess of monomer loading. Besides, when the G number gets bigger, the chromatographic separation
time gets longer [16].

b) Convergent method. It is a sharp contrast method with the divergent method. The convergent method is created to overcome the divergent method's shortages [3], such as incomplete terminal group reaction and difficulties in purification [17].

3. Dendrimers and Dendrimer Derivatives

3.1. PAMAM dendrimers.
This is the most deeply studied dendrimers currently. It can deliver drugs and genes through its cavities. However, the cytotoxicity above G5 is concerned [12]. To overcome this, surface modification with PEG is applied. The PEGylated PAMAM dendrimers have the widest potential for drug and gene delivery.

3.2. PPI Dendrimers
Poly-(Propyleneimine) dendrimer is a type for drug delivery. The amino terminal groups give water solubility to the molecule. It has a lower drug loading capacity than PAMAM dendrimers [13]. The surface modification methods have been applied, such as PEGylation and acetylation [14].

3.3. PLL Dendrimers
Poly-L-lysine (PLL) dendrimers contain lysine residues. It has good biocompatibility, so it is used for gene delivery. The higher generation of PLL has better gene transfection [15].

4. Dendrimers for gene delivery
Gene therapy is a promising therapy for the tumour that was developed in the 1990s. It aims to delete, replace, or modify abnormal genes in tumour cells by introducing nucleic acid segments into the cells [18]. However, as large hydrophilic molecules, nucleic acids cannot easily penetrate cell membranes. Besides, they can be degraded by nucleases, which means they would be fragile in the bloodstream [19]. Therefore, a gene delivery system is necessary for successful gene therapy. Generally, the gene delivery agents can be divided into viral and non-viral vectors. Although possessing higher transfection efficiency, viral vectors have potential immunological and oncological issues limiting their clinical use. In contrast, non-viral vectors have less immune response and are easier to fabricate and modify.

Dendrimers with positively charged skeleton, including PAMAM, PLL, and PLL, are suitable non-viral vectors for gene delivery. Their positive charge allows them to form a stable complex with DNAs through electrostatic interaction, which can penetrate cell membranes and reach the nucleus. In gene delivery applications, the transfection efficiency of dendrimers is a critical concern. Generally, high-generation dendrimers show higher gene transfection efficiency than low-generation ones. However, the tendency of cytotoxicity against generations can be the opposite in some cases. Therefore, different modifications have been applied to improve dendrimer vectors' performance.

4.1. PAMAM dendrimers
PAMAM dendrimers are currently the most interesting dendrimers among all the dendrimers. As carriers for nucleic acids, they can release nucleic acids in cells with the "proton sponge" effect. However, issues including cytotoxicity and load efficacy also exist. Many novel modification strategies have been proposed, including modifications to their inner and outer surface and them as a whole [19].

It has been revealed that PAMAM dendrimers with positive charges on their surface have better permeability to cell membranes comparing with their anionic and neutral counterparts, and therefore higher transfection efficiency. However, such a cationic surface also renders high cytotoxicity. It has been reported that functionalization of their surface amine group can reduce cytotoxicity. Based on that, Patil et al. synthesized internally quaternized and surface modified PAMAM dendrimers for siRNA delivery. The internal quaternary amine can form a stable complex with siRNA, while the acetylated surface possesses lower cytotoxicity than the -NH₂ surface. The delivery system was tested on A2780
human ovarian cancer cells, indicating that the modified system could be internalized by the cells, while the control groups could not [20].

As much research focused on single-generation dendrimers, super structured dendrimeric nanoconstructs (SDNs) are another emerging pathway for gene delivery. Such strategy uses single-generation dendrimers as building blocks to form nanoarchitectures with higher complexity, including core-shell tecto dendrimers, dendrimer dumbbells, dendrimer nanoclusters, dendrimer-templated nanoclusters, and dendrimer nanogels [21]. Liu et al. proposed a strategy that crosslinks G2 PAMAM dendrimers with linkers containing disulfide to construct a supramolecular structure for gene delivery. Since the linker's disulfide bond can be degraded in the cell cytoplasm, lysosomes, and endosomes, the nanocostruct breaks into single dendrimers and releases DNAs in the cells. Tests on HeLa and HEK293 cell lines show that the product possesses higher transfection efficiency and lower cytotoxicity than G2 or G5 PAMAM dendrimer alone [22].

4.2. PPI dendrimers

High-generation dendrimers usually have better complexation with DNAs than low-generation ones, while they also render higher cytotoxicity and limited synthesis and purification. A way to assist the assembly of low generation dendrimers and DNAs may give a system with low cytotoxicity during high loading. Chen et al. reported a novel strategy that uses Au nanoparticles to help assemble G3 PPI dendrimers and DNA/siRNA while not including Au nanoparticles in the final complex. This process's mechanism is still under study, while it is hypothesized that this is due to the competing affinities of nucleic acids and Au for the amine groups of PPI dendrimers. Such strategy prevents Au nanoparticles' potential toxic effect, and the so-produced nanoparticles have mRNA silencing efficiency on A549 human lung cancer cells even higher than G5 PPI dendrimers [23].

5. Dendrimers in Drug Delivery

Drug therapy is thought to be one of the most effective ways in cancer therapy, mostly used to stop cancer cells from spreading, slow down their growth, and even destroy cancer cells [24]. Drug therapy includes chemotherapy, hormonal drug therapy, immunotherapy, and targeted therapy, each of these methods requires a system to deliver drugs to specific tissues or cells. Various anticancer drugs are hydrophobic, including paclitaxel (PTX), camptothecin, 5-fluorouracil, methotrexate, and DOX free base, which cause difficulties in delivery for their administration [25].

The control of dendrimers' properties is easy to achieve, including size and structure, solubility, monodispersity, and the various options of terminal functional groups [1]. Both chemical and physical interactions are applied as drug delivery strategies [26]. As for physical interactions, dendrimers use non-covalent associations, including hydrogen bonds, electrostatic interactions, and hydrophobic to entrap the drugs, which can also be called physical encapsulation of the drugs. Besides, drugs with poor solubility can be carried by dendrimers for their special internal cavities, which are hydrophobic. When the labile linkages are cleaved upon exposure to specific environments, the drug will be released at the target site. In a word, it has been proved that dendrimers can play the role of promising platforms for anticancer drugs [27-30].

This section will be divided into three parts to present a summary of the main studies of the commonly used dendrimers for drug delivery, including PAMAM, PPI, and PLL.

5.1. PAMAM Dendrimers for Drug Delivery

Polyamidoamine, also known as PAMAM, is a type of dendrimer for drug delivery. It is often used as a versatile and reproducible nanocarrier that loads drugs. With the specifically targeted ligands on cancer cells' surface, PAMAM can recognize the specific receptors and release the drugs. (Fig.1.) The preparation of PAMAM conducts several successive synthetic reactions. This process is easy to control the size of PAMAM, which leads to excellent uniformity. Large amounts of studies have concentrated on PAMAM as drug carriers, as that will be mentioned below.
DOX has good efficacy as a widely used anticancer drug. However, due to its systemic side effects, especially cardiomyopathy, the PAMAM-based drug delivery system has been designed to reduce the toxic effects of DOX and keep the high efficacy at the same time [31-32]. To prevent the accumulation of drugs in the lung, DOX-dendrimer conjugates were prepared, reducing the metastatic lung burden with its administration [30]. In these conjugates, DOX is conjugated to the surface of PAMAM through acid-sensitive hydrazone bonds. Additionally, this conjugation contributes to the development of stimuli-sensitive carriers releasing their cargo when exposed to a low pH environment (tumor microenvironment or endosomal vesicles) [33].

There are some other examples of PAMAM dendrimers used in drug delivery. The G4 PAMAM (PAMAM dendrimers of 4th generation) has been proved to conjugate PTX through a glycine-phenylalanine-leucine-glycine peptide linker. According to the experiments results, free PTX has much higher cytotoxicity compared to PTX-dendrimer conjugate (PGD) mentioned above in kidney cells, which makes it possible to deliver PTX to kidney cells for kidney cancer therapy [34]. Apart from PGD, G4 PAMAM can be applied in active targeting therapy as well [34, 36]. In the PTX delivery for active targeting therapy, PEG is used as the linker in the encapsulating process of docetaxel (DTX) that is modified with trastuzumab (TZ) onto the surface of G4 PAMAM [35]. This special molecule's uptake ratio has been proved to be 70% higher than that of free DTX in tumors [36].

With the surface that can be easily modified with different types of molecules, PAMAM dendrimers can improve the effects and efficiency of drug delivery for cancer therapy.

5.2. PPI Dendrimers for Drug Delivery
Polypropylene imine dendrimers (PPI), as shown in Figure 2, are also known as Astramol dendrimers. It has aroused attention because of its large surface and the various functional groups located in its end that may contribute to the binding with other molecules, especially drugs.

Melphalan, a type of chemotherapy agent, can inhibit the synthesis of DNA and RNA. In this case, Melphalan shows tumor growth inhibition, which is a special method for cancer therapy. According to the researchers' studies, Melphalan encapsulated in PPI show improved inhibition in the tumor cells of BALB/C mice. Also, cancer-targeting ability increased with PPI dendrimers modified with folic acid [38,39].

In another research, G4.5 PPI dendrimers were developed to achieve tumor growth inhibition. This type of dendrimers is carboxylic acid terminated to encapsulate PTX and conjugate the monoclonal antibody mAbK1. mAbK1 can target a special protein, mesothelin protein, which is overexpressed in specific cancer cells but not expressed in most normal cells. According to the experimental data, mAbK1-PPI-PTX showed a much higher ratio of tumor growth inhibition. Besides, the results indicated that the concentration of targeted formulations was 7-times higher than that of free PTX in cancer cells, which proved that targeted PPI dendrimers could improve biocompatibility [40].
With the large surface and many different functional groups, PPI dendrimers can help improve the effects and efficiency of drug delivery for cancer therapy.

5.3. PLL Dendrimers for Drug Delivery

Polylysine, also known as PPL, is another type of dendrimers applied in drug delivery for cancer (Figure 3). Although most researchers choose PAMAM and PPI for drug delivery research, PLL also shows excellent potential in this field [41-44].

![Figure 3. Molecular structure of PLL](image)

According to several studies, researchers have concentrated on the potential of PLL as the carriers for DOX. G6 PLL shows good antiangiogenic activity in vivo. As a result, compared to free DOX, PLL and DOX's association has deeper penetration in the prostate cancer cells, which leads to tumor growth inhibition [41]. Besides, PLL with a small size (less than 10nm) can change the tumor penetration in both vitro and vivo, which may help drugs affect cancer cells [42]. In BALB/cN mice model, PLL-DOX modified with hydrophobic pentapeptides that used PEG as the linker improved tumor accumulation through the EPR effect, while a hydrophobic cavity was created by the oligopeptide link to increase DOX encapsulation [46].

The research results mentioned above reflect people's expectation of dendrimers' potential to be applied in cancer therapy. However, the cost of manufacture and quality control problems should be solved, and the long-term effects of dendrimers on human health should be evaluated before such products can reach the market.

6. Conclusion

Dendrimers can be applied in cancer treatments, including chemotherapies and gene therapies. In chemotherapies, anti-tumour drugs such as DOX and PTX can have high cytotoxicity to normal cells as well as tumour cells, limiting their clinical use. The surface-modified dendrimers can conjugate anti-tumour drugs through chemical or physical interaction and deliver them precisely to the target site, with reduced cytotoxicity and higher cell uptake. As for gene therapy, the prevention of nucleic acid degradation during delivery and the increase of cell uptake are the major concerns. Therefore, novel modification strategies have been developed to improve dendrimers' performance as nucleic acid carriers, including surface modification, formation of SDNs, and Au assisted complex formation. In conclusion, dendrimers have great potential in cancer therapies, while more novel modifications can push them further into clinical applications.

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