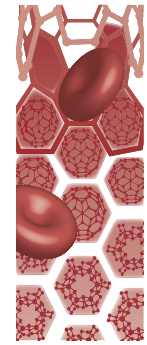
Review

For reprint orders, please contact: reprints@futuremedicine.com

Nanomedicine



Application of dextran as nanoscale drug carriers

Gangliang Huang*,[1] & Hualiang Huang**,[2]

[1]Active Carbohydrate Research Institute, Chongqing Key Laboratory of Inorganic Functional Materials, Chongqing Normal University, Chongqing 401331, China

[2]School of Chemistry & Environmental Engineering, Wuhan Institute of Technology, Wuhan 430073, China

*Author for correspondence: huangdoctor226@163.com

**Author for correspondence: hlhuang@wit.edu.cn

Dextran is a kind of biocompatible, nontoxic and nonimmunogenic biological substance that has been widely used in drug-delivery systems. With further research and understanding of dextran and its derivatives, people can more precisely control the sequence of dextran by chemical and biosynthetic methods as needed, and modify various structures to improve the properties of dextran, such as hydrophilicity, hydrophobicity, temperature sensitivity, pH sensitivity and ionic strength sensitivity, which will further expand the application of dextran and its derivatives in drug-delivery systems. Herein, the application of dextran and its derivatives in gene transfection and drug delivery was summarized and analyzed, and the problems were studied. At the same time, its application prospects are forecasted.

First draft submitted: 8 September 2018; Accepted for publication: 5 November 2018; Published online: 5 December 2018

Keywords: applications • biomaterial • carrier • dextran • gene transfection • nanosystem

The drug-delivery system prepared under nanotechnology has the characteristic of small volume, which is favorable for the adsorption and phagocytosis of drugs by cells, thereby promoting the body's absorption of drugs [1]. In addition, it has a larger specific surface area and can carry or couple more functional groups or active centers. So, the local concentration of drug in the target is high, thereby improving the efficacy [2]. Moreover, it can adsorb, encapsulate, disperse or couple active molecules into the system. Therefore, the drug can be effectively protected from enzyme digestion and immune clearance on the way to the target. It can not only transport hydrophilic molecules but also transport hydrophobic molecules that are not suitable for intravenous injection [3]. The construction of a drug-delivery system is an extremely important use of polymers. Many polymers have been widely used in drug-delivery systems [4]. Degradable polymers that are easy to prepare and modify are often candidate carriers for drug delivery. The acetals, orthoester, hydrazones, imines and *cis*-aconityl are the acid-labile groups, which can cleave in slightly acidic conditions. These acid-labile groups have been used to create polymer architectures or polymer–drug conjugates, which can degrade under lysosomal and endosomal conditions. Thus, it can trigger to quickly release drugs or DNA [5]. The nanoscale drug carriers designed based on these polymer materials have good biocompatibility, can not only improve the stability of drugs in the blood but also have the functions of targeting, sustained release and controlled release, and can significantly prolong the action time of drugs [6]. They can greatly improve the pharmacodynamics and pharmacokinetics of the drugs, and they can also reduce the number of patients taking the drug and increase compliance, which are beneficial to the treatment of chronic diseases such as diabetes and coronary heart disease [7]. Despite the great progress of nanocarriers, various drug-delivery systems were born in the laboratory, and *in vitro* and animal experiments also showed good results. However, exploring a safe, effective and stable drug-delivery system suitable for clinical application remains a challenging problem in pharmacy. Natural polymer materials tend to have the advantages of low toxicity and low cost. Among them, dextran is a common biological macromolecule, which is a polymer of monomeric α-D-glucose. Its backbone is linked by α-(1→6) glycosidic bond, and the starting end of the branched chain is α-(1→4) glycosidic bond or α-(1→3) glycosidic bond, which is attached to the backbone [8]. Its molecular size and degree of branching are closely related to its source. Dextran is easily chemically modified, and various

Future Medicine

glycoconjugates can be derivatized by reactions such as etherification, esterification, amidation and oxidation. In particular, dextran has excellent water solubility, biocompatibility and biodegradability, it also enhances the stability of the drug-delivery system and prevents it from accumulating in the blood circulation [9]. These advantages provide a material basis for the design and preparation of new delivery systems. Inhibition of complement activation is its important biological activity. Moreover, polysaccharides are the important elements in constructing functional drug-delivery systems. Polysaccharides such as dextran, chitosan, hyaluronic acid and heparin sulfate have ligand activity. When the system is modified by these polysaccharides, the receptor on the target cell specifically interacts with them to trigger phagocytosis, which is an important application of active targeted drug delivery [10]. For these reasons, polysaccharides are functional molecules that modify or coat the delivery system. In view of the good biocompatibility, biodegradability, nonimmunogenicity and high affinity for tumor cells, hyaluronic acid and its derivatives have also attracted attention as novel drug carriers [11]. Recently reported dextran-based drug-delivery systems include not only macromolecular graft modifications from chemical synthesis but also noncovalent bond-based supramolecular complexes. It showed that the photosensitive microcapsules had great potential for biomedical application [12,13]. Among them, some nanocarriers make full use of the intracellular microenvironment and external cell stimuli, and have the function of controlled release to drugs, which can increase the bioavailability and improve the efficacy of drugs.

Gene transfection

DNA, especially RNA, are highly biodegradable macromolecules, so the key to successful gene therapy lies in the delivery of gene vectors, ensuring the safe delivery of nucleic acids to the target and enabling efficient expression. Although viral vectors have excellent transfection efficiency, their toxicity and immunogenicity cannot be ignored [14]. In view of the high safety and low cost of many polymer materials, polycationic macromolecules are considered to be promising delivery vehicles for nucleic acid drugs. Cationic polymer vehicles for gene delivery can effectively resist premature serum degradation, but they often have difficulty in releasing their nucleic acid cargoes. The switchable polymers are the good solution to address the question, and have the potential for therapeutic agent delivery [15]. In order to improve the transfection efficiency and find a suitable carrier for clinical use, people synthesized a variety of polycationic compounds for the delivery of nucleic acids. Dextran and its derivatives are also subjects of concern and investigation [16].

In order to reduce the toxicity of polylysine and inhibit its nonspecific adsorption on the cell surface, the polylysine was modified with dextran, the obtained grafted macromolecule could effectively promote the differentiation and maturation of mesenchymal stem cells, and could also deliver plasmid DNA to the mesenchymal stem cells for efficient expression. It proved that the aldehyded dextran and ε-poly(L-lysine) had great potential as noncarrier for gene transfer [17]. Polyethylenimine (PEI) is a commonly used vector for gene transfection, and many *in vitro* studies have been reported. PEI is one of the cationic polymers for gene delivery, but its application is limited because of its drawbacks. The glycoconjugates were prepared by coupling dendritic PEI with dextran, which had better biocompatibility than PEI. Both *in vitro* and *in vivo* experiments showed the ideal transfection efficiency. So, it proved that Dextran-g-PEI had great potential for gene-delivery systems [18]. Green fluorescent protein could be highly expressed *in vivo*, and was mainly distributed in important organs such as the lung, spleen and liver in rats [19]. Previous studies indicated that heparanase was an important target for the treatment of choriocarcinoma cells [20]. It was found that dextran-coated magnetic iron tetroxide nanoparticle was a good carrier for transporting heparanase antisense nucleic acids. Namely, it proved that Fe_3O_4-dextran-anti-β-human chorionic gonadotropin nanoparticles had potential as a gene vector for choriocarcinoma-specific targeting. [21]. The cell proliferation activity and function of the dextran magnetic nanoparticles after transfection were slightly better than those of the liposomes, and it was effectively demonstrated that the cytotoxicity of the dextran magnetic nanoparticles was lower than that of the liposomes. Therefore, dextran magnetic nanoparticles could be used as one of the effective gene carriers. With the development of nanotechnology and medical polymer materials, magnetic nanoparticles have a good application prospect as a gene and drug carrier, which has attracted widespread attention. Dextran magnetic nanoparticles are the latest research in the field of guiding drugs and medical nanomaterials at home and abroad. Under the action of external magnetic field, it can guide the loading of substances in the body to move and locate, and the concentration of dextran magnetic nanoparticles can be as high as 100% in the target zone. Since dextran magnetic nanoparticles are the smallest diameter of the targeted preparations, they have a unique interfacial effect, exhibiting many excellent properties and new functions, which can escape the phagocytosis of macrophages *in vivo*. Through their combined ligands, selective localization and active targeting can be carried out.

Synergistic introduction of target organs, target cells and even intracellular target structures can be accomplished by synergistic magnetic targeting of dextran magnetic nanoparticles. In addition, the dextran magnetic nanoparticles have good biocompatibility and biosolubility, are nontoxic and have no side effects, and have good stability in solution. Compared with existing carriers, it is safe, specific and feasible. More importantly, the active groups on the polymer dextran are surface-modified to simultaneously load or encapsulate multiple functional molecules (drugs, enzymes, antibodies, peptides, DNA and RNA) with good compatibility. Therefore, the multifunctional magnetic nanomaterial composite can be prepared, and the ideal positioning target molecule can be selected to achieve the dual positioning of magnetic localization and biological orientation, so that the therapeutic medium is ideally located, stably and evenly distributed in the tumor lesion.

Antisense nucleic acids could be efficiently expressed in choriocarcinoma cells JEG-3 and could significantly inhibit JEG-3 proliferation [22]. Leukocytes have long been considered as cells that are difficult to transfect, and many efficient transfection reagents for other cells are inefficient for leukocytes [23]. Amini's group found that the combination of dextran and PEG-modified spermine had a good effect on the transfection of leukocytes, and it is necessary to further improve the delivery efficiency of PEGylated-dextran-spermine [24]. The polycationic polypeptide R5H5 was modified with dextrans of different molecular masses (10, 20 and 70 kDa), and found that the molecular mass of dextran and the degree of substitution to R5H5 significantly affected transfection efficiency and cytotoxicity. A certain molecular mass of dextran was conjugated with R5H5. When the degree of substitution was 40%, it showed the best transfection efficiency and low toxicity. It showed that the dextran-R5H5 with the low molecular mass of dextran and the high substitution degree of R5H5 would be promising for efficient gene therapy [25]. When using dextran to modify other vectors, it was also necessary to examine the relationship between molecular weight/modification rate and transfection efficiency. They also used this glycoprotein to successfully deliver the single-stranded miRNA to HepG2 cells under normal conditions for efficient transfection. It showed that the dextran–peptide complex should be promising for the efficient miRNA-based therapy [26]. It was found that different ways of covalently linking dextran with linear PEI also affected transfection efficiency, and produced different cytotoxicity. Although reductive aminidation was the most common chemical reaction of polysaccharide-modified polymers, they believed that the amide bond was a more suitable way to connect than the reductive aminidation. It showed that the linking method of linear PEI to dextran had a obvious effect on the physicochemical properties of DNA/polymer complexes, the biocompatibility and the transfection efficiency [27]. Yeo's team dropped the dextran-spermine-DNA nanocomplexes into the nasal cavity of rats to achieve targeted delivery to the lungs. The reporter gene was expressed only in the lungs, which provided a valuable experimental basis for the treatment of lung disease. It showed that the dextran-spermine/pDNA had mild toxicity in the mouse lungs [28]. A multifunctional nanoadministration vehicle consisting of dextran, disulfide-bearing polyamines and folic acid was linked by amide bonds. Folic acid was the ligand of folate receptor on the surface of cancer cells. The reducing microenvironment in cancer cells could cut off disulfide bonds and help release the carried nucleic acids. It proved that the disulfide-based cationic dextran system would have a high potential for intravenous gene delivery, which was toward cancer gene therapy [29]. Dextran could enhance the stability of nanodosing system and avoid sinking in the blood. *In vivo* experiments in rats showed that the novel vector had higher transfection efficiency and better safety than commercial transfection reagent PEI and liposomes. Understanding the biological barriers as well as the structure–activity relationship between lipids and polymeric carriers is the key to improving effective nucleic acid therapy [30]. Cyclodextrins were the most commonly used host molecules for the construction of supramolecular systems [31]. Their polyamino or polythiol derivatives could form a supramolecular system by self-assembly with hydrophobic group-modified dextrans, which could effectively deliver nucleic acids for efficient transfection. Chen *et al.* synthesized polyaminodextran as an effective carrier for the delivery of choline kinase interfering RNA, which could effectively inhibit the synthesis of choline kinase in cancer cells. Namely, this nanocarrier could deliver choline kinase siRNA for choline kinase inhibition in cells [32]. It was confirmed by *in vitro* and *in vivo* mouse experiments that the glycoconjugate formed by linear PEI and dextran (5 or 10 kDa) with disulfide bond had excellent safety and good efficacy for gene delivery and cancer treatment. Based on this, they believed that this was a derivative of dextran that had clinical application prospects [33].

Cationic dextran can improve the stability of DNA and penetrate cell membrane through the action of charge, thus avoiding the degradation of endosomes. Therefore, the study of targeted carrier materials to reduce cytotoxicity and improve the transfection rate has attracted great attention.

10.2217/nnm-2018-0331

Drug delivery

As a new drug carrier, dextran nanoparticles have the characteristics of nontoxicity, good biocompatibility, biodegradability, improving drug stability, changing the route of administration, increasing drug absorption and enhancing the bioavailability of drugs. Therefore, it can be controlled and targeted therapy in the body. According to the structure and properties of dextran, drug-loaded dextran nanoparticles can be prepared by various methods. Dextran has become the focus of research on target and controlled release, and has a broad application prospect. In addition, the surface modification of dextran nanoparticles has the selectivity required by target organs, target tissues and target cells, which can be achieved by using modern molecular design ideas and advanced synthesis techniques.

Micelles are thermodynamically stable colloids formed by the self-assembly of amphiphilic polymers. They are widely used in drug delivery, can increase the solubility of hydrophobic drugs in the body, effectively prolong the action time of drugs and increase the bioavailability of drugs. It proved that the amphiphilic asulacrine-multiseed liposomes could effectively load drug into micelles and improve the retention of drug [34]. The poly(lactic-*co*-glycolic acid) and dextran were used to react by esterification to form a parent graft, which had the function of self assembly to form micelles. It could encapsulate paclitaxel to form a nanosystem suitable for intravenous injection, which had effective antitumor activity with lower toxicity [35]. The supramolecular nanocarriers prepared with dextran had a very high encapsulation efficiency for doxorubicin with excellent monodispersity and stability, also had good biocompatibility. Release of high-dose doxorubicin in the acidic microenvironment of cancer cell endosomes or lysosomes significantly increased the efficacy of anticancer drugs and reduced the toxic side effects of doxorubicin. It provided a deeper understanding to the mechanism that acidity-responsive delivery could enhance the chemotherapy performance (Figure 1) [36].

The dextran-based doxorubicin was a prodrug, the two were coupled via a hydrazine group and could slowly hydrolyze and release doxorubicin under weak acid conditions. The nanoscale prodrug could significantly reduce the toxic side effects of doxorubicin and increase its bioavailability. Furthermore, folic acid modification could improve its targeting, and the administration system was mainly distributed in the liver of rats [37]. It was found that dextran-coated supermagnetic iron oxide nanosphere was a excellent carrier of doxorubicin, which had no toxic side effects in animals and could inhibit the growth of rat tumors. It was hopeful to develop into clinical use of chemotherapeutic agents [38]. In addition to the functions of self-assembly and molecular recognition, supramolecular hydrogels also have phase transition reversibility in response to external physical and chemical factors, and are emerging as high-molecular drug sustained-release materials. It indicated that the supramolecular hydrogel system would be promising for combination therapy, which had good bioavailability and minimal side effects [39]. The supramolecular hydrogel prepared by using dextran has been preliminarily confirmed to be able to efficiently deliver insulin, which provides an experimental basis for the development of oral protein pharmaceutical preparations. It proved that the microhydrogels should be suitable for self-regulated insulin delivery [40]. Curcumin exhibits significant anticancer activity as well as strong fluorescence, so it is a potential anticancer drug and bioimaging agent. Due to poor water solubility and low bioavailability, it has not yet been clinically applied [41]. The amphipathic nanospheres were prepared with self-assembly properties using curcumin and dextran, which had excellent water solubility and high capacity for drug loading. Importantly, the nanoscale drug-delivery system was readily ingested by HeLa cells and exhibited green fluorescence in living cells. It indicated that the dextran-curcumins nanoparticles would be promising for curcumin-based cancer theranostics with high efficacy [42]. Similarly, the dextran-based curcumin was synthesized, which exhibited excellent targeting of hepatocytes, had better safety and bioavailability than monomeric curcumin. So, it indicated that the dextran-based nanosized drug carrier would be a promising carrier for drug-delivery [43]. The natural product 2′-hydroxy-2,4,4′,5,6′-pentamethoxychalcon (Rubone) from *Astragalus membranaceus* could specifically regulate the expression of miRNA-34a in hepatoma cells and was considered as a new type anticancer drug. It showed that how rubone acted as an efficient small-molecule modulator of miR-34a for reversing the chemoresistance and further enhancing the therapeutic efficacy of paclitaxel for paclitaxel-resistant prostate cancer [44]. To improve its solubility and increase its clinical application potential, the micelles were prepared with PEI, dextran and polycyclohexanolide. *In vitro* experiments demonstrated that it could effectively transport Rubone into hepatocytes, significantly promote the synthesis of miRNA-34a, effectively inhibit the proliferation of hepatoma cells and trigger cancer cell apoptosis. After administration to the tail vein of mice, Rubone was concentrated in the tumor tissue, the growth of tumor was significantly inhibited and the biocompatibility of agent was also good. It indicated that carboxymethyl dextran-stabilized PEI-poly(ε-

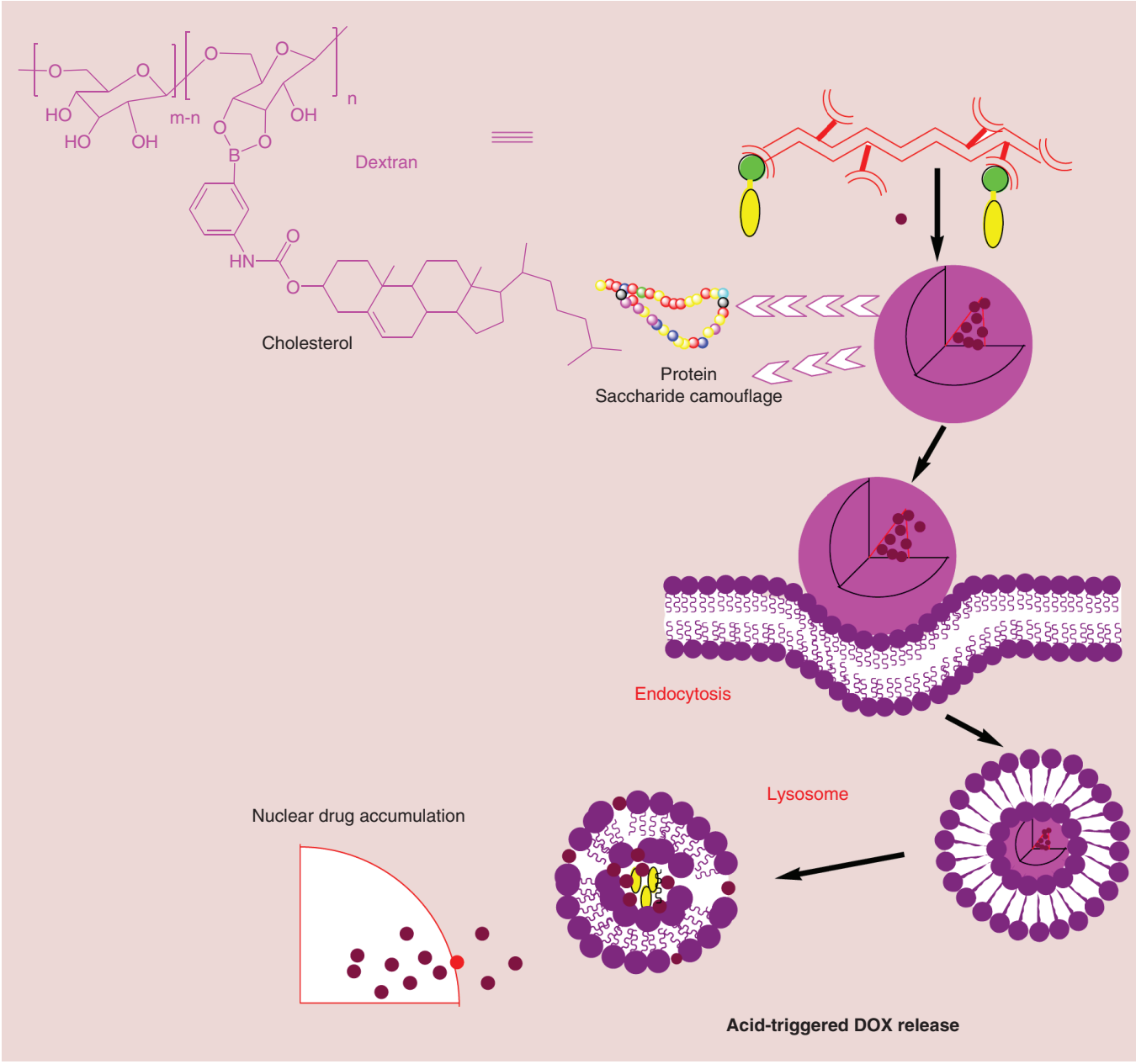


Figure 1. The reversible pH-dependent dextran/phenylboronic acid modified cholesterol nanoassembly for lysosome-acidity-targeting bioresponsive drug delivery.
DOX: Doxorubicin.

caprolactone) nanoparticles might serve as a novel approach to small-molecule-modulator-mediated miRNA-34a restoration for hepatocellular carcinoma therapy [45]. The dextran-based paclitaxel was obtained by esterification reaction, which had strong ability to respond to acid. Under the physiological pH of 7.4, the drug could be slowly released. The release of paclitaxel was further accelerated by simulating the microenvironment of cancer cells (pH < 6.5). *In vivo* experiments in mice showed that dextran-based paclitaxel had stronger inhibitory activity against cancer cells and decreased paclitaxel toxicity. So, the carboxymethyl dextran-based conjugate might be a promising carrier of docetaxel for cancer therapy [46]. A similar pH-responsive drug-delivery system was also reported. Its carrier was poly(lactic-*co*-glycolic acid) modified by a combination of dextran and histidine, which could effectively target the delivery of paclitaxel to tumor tissues and and produce a good effect in mice. It proved that the biocompatible pH-responsive dextran-*g*-poly(lactide-*co*-glycolide)-*g*-histidine micelles would be a novel

10.2217/nnm-2018-0331

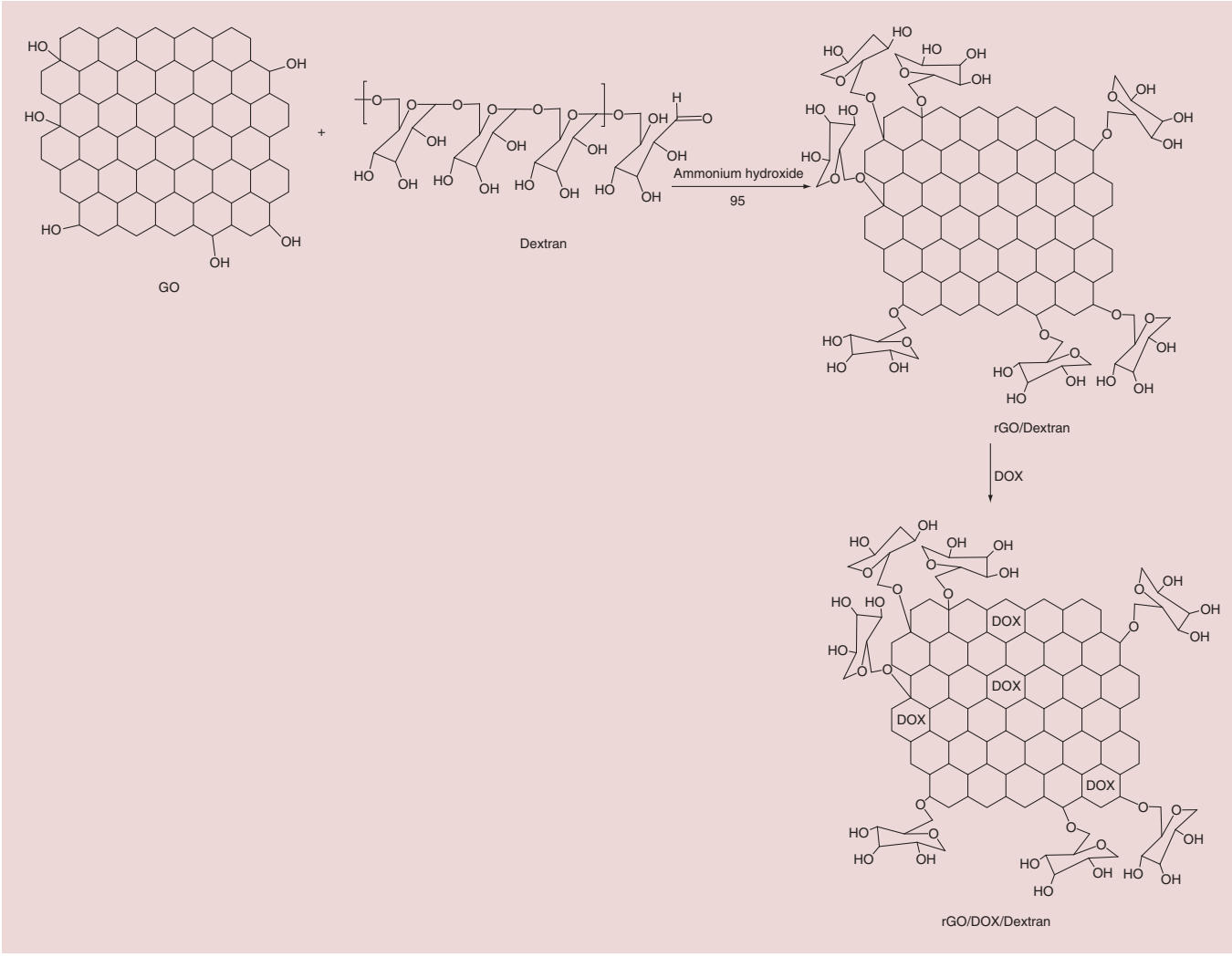


Figure 2. The synthesis route of rGO/dextran and the DOX loading.
DOX: Doxorubicin; rGO: Reduced graphene oxide.

nanocarrier for the intracellular paclitaxel delivery [47]. Many diabetics do not follow insulin injections and effective oral insulin preparations are more popular. The Alibolandi's group synthesized amphiphilic macromolecule. It was a graft modification of poly(lactic-*co*-glycolic acid) and dextran (5000 and 25,000), which could encapsulate insulin into nanosphere. Diabetic model tests in rats showed that this new type of insulin delivery system was an oral dosage form. So, insulin-loaded and self-assembled dextran-poly(lactic-*co*-glycolic acid) polymersomes would be a promising oral insulin carrier system [48]. The dextran-based polylactide was prepared, which could effectively deliver docetaxel in rats. The method could not only control the drug-release but also enhance the potential of pharmacokinetic and pharmacodynamic for docetaxel and other similar anticancer agents [49]. It was found that nanoscale-reduced graphene prepared with dextran as a reducing agent and coating agent had excellent water solubility and biocompatibility, and was suitable for the delivery of anticancer drugs such as paclitaxel. Induced by infrared light, it had good anticancer effect. With the local specific chemotherapy and external near-infrared photothermal therapy, the reduced graphene oxide/DOX/dextran had the higher therapeutic efficacy, which proved the reduced graphene oxide-based nanoparticle had great potential for cancer treatments (Figure 2) [50].

Sericin is a kind of luminescent protein from silkworm. The nanohydrogel was synthesized by coupling sericin and dextran through hydrazone group. It was a suitable carrier for intravenous injection of paclitaxel, which could effectively transport paclitaxel and inhibit the growth of tumor in mice. In particular, the optical properties of sericin ensured real-time tracking and detection of *in vivo* drug-delivery system [51]. Cao *et al.* modified camptothecin and

doxorubicin with dextran, respectively. These two prodrugs used medicinal hydrazone groups or disulfide bonds as coupling functional groups to release the active drugs in the presence of an acidic or reducing agent. They had better anticancer activity than monomeric drugs *in vivo* and *in vitro*. The modification of dextran could effectively reduce the toxic side effects of anticancer drugs. Multiple drugs can effectively treat cancer in combinatory therapy because they can efficiently reduce the multidrug resistance of tumor cells. It showed that the anticancer prodrug design platform would be useful to treat the various tumors [52].

The reactive oxygen species-responsive dextran derivatives can be used as nanocarriers for the delivery of proteins and peptides [53,54]. In addition, the acetal-modified dextran as pH-responsive polymer has also been used in drug delivery [55,56].

Conclusion

With the further study and understanding of dextran and its derivatives as well as the discovery of more functional dextran derivatives, one can more precisely control the sequence of dextrans by chemical and biosynthetic methods as needed. The various modifications of its structure can improve the characteristics of dextran, such as hydrophilicity, hydrophobicity, temperature sensitivity, pH sensitivity and ionic strength sensitivity. This will further expand the applications of dextran and its derivatives in drug-delivery systems.

Future perspective

Dextran is a commonly used macromolecule in nanodosing systems, and some of its delivery systems have shown initial results in animal experiments. Unfortunately, the preparation of most drug-delivery systems is cumbersome and it is not easy to scale up production. At present, there are no cases that are suitable for clinical use. Although natural dextrans are widely considered as a safe drug-delivery platform, clinical trials have shown that dextran can cause side effects such as thrombocytopenia and liver toxicity [57]. Therefore, in order to clarify the safety of dextrans, more in-depth and more clinical toxicology studies need to be carried out. Dextran has a wide range of sources. Structural differences such as molecular mass ($>10^6$ Da) and degree of branching can also lead to significant differences in biological activity and efficacy [58]. Dextran from microorganisms may be contaminated with potentially immunogenic endotoxins, resulting in the weakening or counteracting of dextran's efficacy [59]. Therefore, a standardized separation and purification process needs to be established. The fate and changes of dextran in the body are not completely clear. It is necessary to clarify its changes in the morphological structure, metabolism and function of the drug target site, which helps guide the design and modification of dextran-based drug delivery vehicles [60]. In any case, dextran is a promising biomaterial. With the deep understanding of dextran and the emergence of new functional dextran derivatives, it will be used more and more in nanoscale drug-delivery systems, and clinically applicable delivery systems may also be available.

Executive summary

- Dextran has excellent water solubility, biocompatibility and biodegradability, and it also enhances the stability of the delivery system and avoids sinking in the blood circulation.
- In order to improve the transfection efficiency and find a suitable carrier for clinical use, people synthesized a variety of polycationic compounds for the delivery of nucleic acids, dextran and its derivatives are also subjects of concern and investigation.
- In any case, dextran is a promising biomaterial. With the deep understanding of dextran and the emergence of new functional dextran derivatives, its application in nanodrug-delivery systems will be more and more, clinically applicable delivery systems may also be available.

Financial & competing interests disclosure

The project was sponsored by the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry (No. 2015-1098). The work was also supported by Chongqing Key Research Project of Basic Science & Frontier Technology (No. cstc2017jcyjBX0012), Foundation Project of Chongqing Normal University (No. 14XYY020), Chongqing General Research Program of Basic Research and Frontier Technology (No. cstc2015jcyjA10054) and Chongqing Normal University Postgraduate's Research and Innovation Project (No. YKC17004), China. Writing support was provided by State Education Ministry. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Parhi P, Mohanty C, Sahoo SK. Nanotechnology-based combinational drug-delivery: an emerging approach for cancer therapy. *Drug Discov. Today* 17(17-18), 1044–1052 (2012).
2. Koo OM, Rubinstein I, Onyuksel H. Role of nanotechnology in targeted drug-delivery and imaging: a concise review. *Nanomedicine* 1(3), 193–212 (2005).
3. Chen X, Liu Z. Dual responsive mesoporous silica nanoparticles for targeted co-delivery of hydrophobic and hydrophilic anticancer drugs to tumor cells. *J. Mater. Chem. B* 4(25), 4382–4388 (2016).
4. Raizada A. Polymers in drug delivery: a review. *IJPRD* 2(8), 1655–1670 (2010).
5. Binauld S, Stenzel MH. Acid-degradable polymers for drug delivery: a decade of innovation. *Chem. Commun.* 44(21), 2082–2102 (2013).

• **Acid-degradable polymers can be used for drug delivery.**

6. Pippa N, Pispas S, Demetzos C. Polymer self-assembled nanostructures as innovative drug nanocarrier platforms. *Curr. Pharm. Des.* 22(19), 2788–2795 (2016).
7. Tuttle RR, Browne CE. Diagnosis, evaluation and treatment of coronary artery disease by exercise simulation using closed loop drug-delivery of an exercise simulating agent beta agonist. *US* US5286252 (1994).
8. Takashima Y, Fujita K, Ardin AC. Characterization of the dextran-binding domain in the glucan-binding protein C of *Streptococcus mutans*. *J. Appl. Microbiol.* 119(4), 1148–1157 (2015).
9. Varshosaz J. Dextran conjugates in drug delivery. *Expert Opin. Drug Deliv.* 9(5), 509–523 (2012).
10. Dheer D, Arora D, Jaglan S. Polysaccharides based nanomaterials for targeted anti-cancer drug delivery. *J. Drug Target.* 25(1), 1–16 (2016).

• **Polysaccharides-based nanomaterials can be used for the targeted anticancer drug delivery.**

11. Huang G, Huang H. Hyaluronic acid-based biopharmaceutical delivery and tumor-targeted drug-delivery system. *J. Control. Rel.* 278, 122–126 (2018).

•• **Hyaluronic acid is a promising drug carrier.**

12. Toman P, Lien CF, Ahmad Z. Nanoparticles of alkylglyceryl-dextran-graft -poly(lactic acid) for drug-delivery to the brain: preparation and *in vitro*, investigation. *Acta Biomater.* 23, 250–262 (2015).
13. Xiao W, Chen WH, Zhang J. Design of a photoswitchable hollow microcapsular drug-delivery system by using a supramolecular drug-loading approach. *J. Phys. Chem. B* 115(46), 13796–13802 (2011).
14. Merdan T, Kopecek J, Kissel T. Prospects for cationic polymers in gene and oligonucleotide therapy against cancer. *Adv. Drug Deliv. Rev.* 54(5), 715–758 (2002).

•• **The cationic polymers are promising in gene and oligonucleotide therapy against cancer.**

15. Cheng Y, Sellers DL, Tan JY. Development of switchable polymers to address the dilemma of stability and cargo release in polycationic nucleic acid carriers. *Biomaterials* 127, 89–96 (2017).
16. Thomas JJ, Rekha MR, Sharma CP. Unraveling the intracellular efficacy of dextran-histidine polycation as an efficient nonviral gene delivery system. *Mol. Pharmacol.* 9(1), 121–134 (2012).
17. Togo Y, Takahashi K, Saito K. Aldehyded dextran and ε-poly(L-lysine) hydrogel as nonviral gene carrier. *Stem Cells Int.* 2013(9), 634379 (2013).
18. Chu M, Dong C, Zhu H. Biocompatible polyethylenimine-graft-dextran catiomer for highly efficient gene delivery assisted by a nuclear targeting ligand. *Polym. Chem.* 4(8), 2528–2539 (2013).
19. Takeuchi K, Sereemaspun A, Inagaki T. Morphologic characterization of green fluorescent protein in embryonic, neonatal, and adult transgenic rats. *Anat. Rec. A Discov. Mol. Cell. Evol. Biol.* 274A(2), 883–886 (2003).
20. Bohlmann MK, Hoerster JC, Bundschuh D. Growth-modulatory effects of Heparin and VEGF165 on the choriocarcinoma cell-line JEG-3 and its expression of heparanase. *Anticancer Res.* 34(12), 7071–7076 (2014).
21. Cai J, Liu H, Zhang Y. Preparation and characterization of magnetic nanoparticles containing Fe_3O_4-dextran-anti-β-human chorionic gonadotropin, a new generation choriocarcinoma-specific gene vector. *Int. J. Nanomed.* 6, 285–294 (2011).
22. Morales-Prieto DM, Schleussner E, Markert UR. Reduction in miR-141 is induced by leukemia inhibitory factor and inhibits proliferation in choriocarcinoma cell line JEG-3. *Am. J. Reprod. Immunol.* 66(S1), 57–62 (2011).
23. Morris VB, Labhasetwar V. Arginine-rich polyplexes for gene delivery to neuronal cells. *Biomaterials* 60, 151–160 (2015).

• **The arginine-rich polyplexes can be used for gene delivery to neuronal cells.**

24. Amini R, Jalilian FA, Abdullah S. Dynamics of PEGylated-dextran-spermine nanoparticles for gene-delivery to leukemic cells. *Appl. Biochem. Biotechnol.* 170(4), 841–853 (2013).
25. Tang Q, Cao B, Lei X. Dextran–peptide hybrid for efficient gene delivery. *Langmuir* 30(18), 5202–5208 (2014).

• **Dextran–peptide hybrid can be used for efficient gene delivery.**

26. Tang Q, Lei X, Cao B. A naturally derived dextran-peptide vector for microRNA antagomir delivery. *RSC Adv.* 5(35), 28019–28022 (2015).
27. Ochrimenko S, Vollrath A, Tauhardt L. Dextran-graft-linear poly(ethylene imine)s for gene delivery: importance of the linking strategy. *Carbohydr. Polym.* 113(9), 597–606 (2014).
28. Yeo WW, Hosseinkhani H, Rahman SA. Safety profile of dextran-spermine gene delivery vector in mouse lungs. *J. Nanosci. Nanotechnol.* 14(5), 3328–3336 (2014).
29. Song Y, Lou B, Zhao P. Multifunctional disulfide-based cationic dextran conjugates for intravenous gene-delivery targeting ovarian cancer cells. *Mol. Pharm.* 11(7), 2250–2261 (2014).
30. Zhu L, Mahato RI. Lipid and polymeric carrier-mediated nucleic acid delivery. *Expert Opin. Drug Deliv.* 7(10), 1209–1226 (2010).

•• **Lipid and polymeric carrier-mediated nucleic acid delivery is very interesting.**

31. Santagapita PR, Mazzobre MF, Buera MP. Impact of supramolecular interactions of dextran-Î²-cyclodextrin polymers on invertase activity in freeze-dried systems. *Biotechnol. Prog.* 31(3), 791–798 (2015).
32. Chen Z, Krishnamachary B, Bhujwalla ZM. Degradable dextran nanopolymer as a carrier for choline kinase (ChoK) siRNA cancer therapy. *Nanomaterials* 6(2), E34 (2016).
33. Zhao J, Wang C, Zhao P. Bioreducible dextran-polyethylenimine conjugates regulate transgene expression distribution *in vivo*. *J. Mater. Chem. B* 3(8), 1529–1536 (2016).
34. Zhang W, Li C, Jin Y. Multiseed liposomal drug-delivery system using micelle gradient as driving force to improve amphiphilic drug retention and its anti-tumor efficacy. *Drug Deliv.* 25(1), 611–622 (2018).
35. Liu P, Situ JQ, Li WS. High tolerated paclitaxel nano-formulation delivered by poly(lactic-*co*-glycolic acid)-*g*-dextran micelles to efficient cancer therapy. *Nanomedicine* 11(4), 855–866 (2015).
36. Zhu JY, Lei Q, Yang B. Efficient nuclear drug translocation and improved drug efficacy mediated by acidity-responsive boronate-linked dextran/cholesterol nanoassembly. *Biomaterials* 52(1), 281–290 (2015).
37. Varshosaz J, Hassanzadeh F, Sadeghi AH. Synthesis and characterization of folate-targeted dextran/retinoic acid micelles for doxorubicin delivery in acute leukemia. *BioMed. Res. Int.* 2014(3), 525684 (2014).
38. Peng M, Li H, Luo Z. Dextran-coated superparamagnetic nanoparticles as potential cancer drug carriers *in vivo*. *Nanoscale* 7(25), 11155–11162 (2015).
39. Li B, Zhang L, Zhang Z. Physiologically stable F127-GO supramolecular hydrogel with sustained drug-release characteristic for chemotherapy and photothermal therapy. *RSC Adv.* 8(3), 1693–1699 (2018).
40. Yin R, Tong Z, Yang D. Glucose-responsive insulin delivery microhydrogels from methacrylated dextran/concanavalin A: preparation and *in vitro* release study. *Carbohydr. Polym.* 89(1), 117–123 (2012).
41. Siviero A, Gallo E, Maggini V. Curcumin, a golden spice with a low bioavailability. *J. Herb. Med.* 5(2), 57–70 (2015).
42. Nagahama K, Sano Y, Kumano T. Anticancer drug-based multifunctional nanogels through self-assembly of dextran-curcumin conjugates toward cancer theranostics. *Bioorganic Med. Chem. Lett.* 25(12), 2519–2522 (2015).
43. Anirudhan TS, Binusreejayan. Dextran based nanosized for the controlled and targeted delivery of curcumin to liver cancer cells. *Int. J. Biol. Macromol.* 88, 222–235 (2016).
44. Wen D, Peng Y, Lin F. Micellar delivery of miR-34a modulator rubone and paclitaxel in resistant prostate cancer. *Cancer Res.* 77(12), 3244–3254 (2017).
45. Deng X, Yin Z, Zhou Z. Carboxymethyl dextran-stabilized polyethylenimine-poly(epsilon-caprolactone) nanoparticles-Mediated modulation of microRNA-34a expression *via* small-molecule modulator for hepatocellular carcinoma therapy. *ACS Appl. Mater. Interfaces* 8(27), 17068–17079 (2016).
46. Han HS, Lee M, An JY. pH-Responsieve carboxymethyl dextran-based conjugate as a carrier of docetaxel for cancer therapy. *J. Biomed. Mater. Res. B* 104(4), 789–796 (2015).
47. Zhang J, Chen K, Ding Y. Self-assemble pH-responsive dextran-*g*-poly(lactide-*co*-glycolide)-*g*-histidine copolymer micelles for intracellular delivery of paclitaxel and its antitumor activities. *RSC Adv.* 6(28), 23693–23701 (2016).
48. Alibolandi M, Alabdollah F, Sadeghi F. Dextran-*b*-poly (lactide-*co*-glycolide) polymersome for oral delivery of insulin: *in vitro* and *in vivo* evaluation. *J. Control. Rel.* 227, 58–70 (2016).

• **Dextran-*b*-poly (lactide-*co*-glycolide) polymersome can be used for oral delivery of insulin.**

49. Raza K, Kumar N, Misra C. Dextran-PLGA-loaded docetaxel micelles with enhanced cytotoxicity and better pharmacokinetic profile. *Int. J. Biol. Macromol.* 88, 206–212 (2016).

50. Hu Y, He L, Ding J. One-pot synthesis of dextran decorated reduced graphene oxide nanoparticles for targeted photo-chemotherapy. *Carbohydr. Polym.* 144, 223–229 (2016).
51. Liu J, Qi C, Tao K. Sericin/Dextran injectable hydrogel as an optically trackable drug-delivery system for malignant melanoma treatment. *ACS Appl. Mater. Interfaces* 8(10), 6411–6422 (2016).
52. Cao D, He J, Xu J. Polymeric prodrugs conjugated with reduction-sensitive dextran-camptothecin and pH-responsive dextran–doxorubicin: an effective combinatorial drug delivery platform for cancer therapy. *Polym. Chem.* 7(25), 4198–4212 (2016).
53. Broaders KE, Grandhe S, Fréchet JMJ. A biocompatible oxidation-triggered carrier polymer with potential in therapeutics. *J. Am. Chem. Soc.* 133(4), 756–758 (2010).
54. Lv W, Xu J, Wang X, Li X, Xu Q, Xin H. Bioengineered boronic ester modified dextran polymer nanoparticles as reactive oxygen species responsive nanocarrier for ischemic stroke treatment. *ACS Nano.* 12(6), 5417–5426 (2018).
55. Bachelder EM, Beaudette TT, Broaders KE, Dashe J, Fréchet JM. Acetal-derivatized dextran: an acid-responsive biodegradable material for therapeutic applications. *J. Am. Chem. Soc.* 130(32), 10494–10495 (2008).
56. Gu Z, Aimetti AA, Wang Q *et al*. Injectable nano-network for glucose-mediated insulin delivery. *ACS Nano.* 7(5), 4194–4201 (2013).
57. Jeavons SM, Ricketts CR, Walton KW. Duration of anticoagulant effect in relation to urinary excretion of dextran sulphate. *Br. Med. J.* 2(5000), 1016–1023 (1956).
58. Kim D, Robyt JF, Lee SY. Dextran molecular size and degree of branching as a function of sucrose concentration, pH, and temperature of reaction of *Leuconostoc mesenteroides* B-512FMCM dextransucrase. *Carbohydr. Res.* 338(11), 1183–1189 (2003).
59. De CH, Matos JA, Bouskela E. Vascular permeability increase and plasma volume loss induced by endotoxin was attenuated by hypertonic saline with or without dextran. *Shock* 12(1), 75–80 (1999).
60. Sun G, Mao JJ. Engineering dextran-based scaffolds for drug-delivery and tissue repair. *Nanomedicine* 7(11), 1771–1784 (2012).