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Application of polysaccharides for surface modification of nanomedicines

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Abstract

Polysaccharides have been used in various biomedical applications due to availability and biocompatibility. In particular, polysaccharides have gained increasing interest in the development of functional nanomedicines as a component to provide a stealth function, improve interactions with target tissues or enable environment-responsive drug release. This review discusses recent advances in nanomedicine engineering based on polysaccharides with a specific emphasis on the rationale, applications and the remaining challenges.

In the treatment and diagnosis of cancer, nanoparticles (NPs) are considered promising carriers of drugs and imaging agents due to their ability to accumulate in solid tumors. A well-known explanation for this property is the so-called enhanced permeability and retention (EPR) effect [1], based on defective tumor vasculature and poor lymphatic drainage [2], which allows for the extravasation of NPs [3] and their accumulation in tumors [1]. For the efficient use of the EPR effect, NPs should be able to circulate in the body, avoiding clearance by the **reticuloendothelial system** [4]. In general, NP clearance from the circulation starts with the **opsonization** of NPs, followed by receptor-mediated phagocytosis [5]. Since hydrophobic and/or charged NPs are prone to opsonization, NPs are usually coated with electrically neutral hydrophilic polymers. This protective surface coating, also known as **stealth coating**, can extend the half-life of NPs significantly [6].

One of the most popular surface modification strategies is to conjugate PEG, a nonionic hydrophilic polymer, on the surface of NPs (PEGylation). Since the early use of PEG in extending the circulation half-life of a protein [7,8], PEGylation has been widely used to protect NPs such as liposomes [9], polymeric NPs [10] and micelles [11] from premature clearance during circulation. Here, the PEG that covers NPs forms a hydrated layer, which allows the NPs to evade opsonization and subsequently phagocytosis [12]. On the other hand, this protective surface also interferes with the desired interactions between NPs and

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targeted cells [13]. For example, PEGylated liposomal doxorubicin showed greater AUC_{plasma} but lower tumor accumulation than those of the non-PEGylated counterpart, indicating the paradoxical effect of PEGylation [14]. A recent review article described that the PEGylated multifunctional envelope-type nano device was less effective in delivering genes into cells than the non-PEGylated device [15]. Furthermore, Lehtinen *et al.* demonstrated, using a computational model, that some targeting moieties could lose the functionality due to the steric hindrance effect of the PEG layer [16]. The increased stability by PEGylation can also hinder the endosomal escape of NPs, a critical step for effective intracellular delivery of nucleic acid therapeutics [17,18]. These challenges have prompted a search for new strategies to protect NP surface. Examples of recent efforts include the use of different polymers of synthetic or natural origin, biomimetic coating and conditional removal of PEG effect [19].

The discussion here focuses on the use of polysaccharides in nanomedicine. Polysaccharides have been widely used in the context of drug delivery and tissue engineering because of biocompatibility, availability and well-established modification schemes [20,21]. Some of the polysaccharides, such as dextran and heparin (Figure 1), have long been recognized as stealth-coating materials due to their ability to inhibit opsonization and complement activation [22,23]. Moreover, several studies demonstrate the ligand activities of polysaccharides such as chitosan, hyaluronic acid and chondroitin sulfate (Figure 1). NPs decorated with these polysaccharides showed more efficient cellular uptake than uncoated NPs, due to their specific interactions with various receptors on target cells [24–27]. For these reasons, polysaccharides have gained increasing interest in the field of nanomedicine as an alternative surface modification strategy. Examples of their applications in various types of nanomedicine follow.

Production of polysaccharide-based NPs

NPs incorporating polysaccharides are produced in various methods, as thoroughly reviewed elsewhere [28,29]. Polysaccharides can form surface layers on core NPs via electrostatic interactions or by anchoring on the NP surface during the formation of NPs (Figure 2a). Alternatively, hydrophilic polysaccharides are grafted with hydrophobic low-molecular-weight molecules such as cholesterol or bile acids to allow for the formation of self-assembled NPs, which carry hydrophobic drugs in the core (Figure 2B). NPs can be made of conjugates of polysaccharides and synthetic polymers, created by various conjugation methods. For example, linear hydrophobic polymers are grafted to a polysaccharide as side chains, creating a branched copolymer. Alternatively, a linear hydrophobic polymer can be conjugated to a polysaccharide terminus to create a linear diblock copolymer. Depending on the configuration of the copolymer, polysaccharides form a loop- (Figure 2c; top) or a brush-style (Figure 2c; bottom) surface layer.

Dextran

Dextran is a water-soluble polymer of (1→6)- α -D-glucose, with branches extending from the (1→3) position and occasionally from (1→4) or (1→2) positions [30]. Dextran is synthesized by bacteria, and the types and molecular weights of dextran vary with bacterial strains and culture conditions [30]. Dextran was first investigated as a plasma substitute in the early 1940s [31]. Due to the biocompatibility and degradability, dextran has long been a biomaterial of choice for various biomedical applications. Dextran has antifouling properties comparable to that of PEG [32] and, thus, been used to shield the surface of polymeric [33,34] or iron oxide NPs [28,35,36]. Dextran coating was shown to extend the circulation time of poly(methyl methacrylate) NPs [22,23]. However, another study reported that dextran-coated poly(caprolactone) NPs could induce complement activation [37]. The

seemingly contrasting results are attributed to the difference of dextran conformation and density on the NP surface [38,39]. A dense brush-like dextran graft provides a steric barrier resistant to protein adsorption [23], whereas flexible dextran loops allow for binding of opsonic components [37]. The effect of dextran conformation on pharmacokinetics and biodistribution of poly(alkylcyanoacrylate) (PACA) NPs has been recently studied [40]. Here, PACA NPs with a dense dextran brush layer avoided liver uptake, whereas PACA NPs covered with dextran loops were rapidly accumulated in the liver [40]. It is noteworthy that the dextran-coated stealth PACA NPs accumulated in well-vascularized organs such as the heart and lungs in less than 48 h, a time typically needed for organ distribution of PEGylated NPs [40].

Heparin

Heparin is a linear polysaccharide with a repeating disaccharide unit of 1,4-linked uronic acid [α -D-glucuronic or L-iduronic acid] and D-glucosamine residues [41]. Heparin is one of the most negatively charged natural products [42] and implicated in various biological functions such as allergy, inflammation [43] and **anticoagulation** [42]. Its anticoagulant effect is initiated by the binding of heparin to antithrombin III and conformational change of the protein [42]. The activated antithrombin III functions as an inhibitor of thrombin and other serine proteases in the coagulation cascade [42]. Heparin is clinically used for extracorporeal procedures requiring anticoagulation and the treatment of thrombotic conditions [42]. In addition, several studies report antiangiogenic effects of heparin and its derivatives. For example, heparin and its fragments administered along with steroids show antiangiogenic effects [44,45]. 6-O-desulfated heparin was found to interfere with binding of FGF-2 to the receptor and, thus, inhibit FGF-2 induced **angiogenesis** [46]. Heparin and its modified version (periodate-oxidized and borohydride-reduced heparin) showed the potential to reduce lung metastasis by competitive inhibition of the cancer cell attachment to subendothelial matrix of lung capillaries [47]. To suppress tumor growth by site-specific inhibition of angiogenesis, heparin was conjugated with targeting ligands such as folate [48] and cyclic RGD peptide [49].

While the biological functions of heparin warrant the exploration as an active ingredient, the use of heparin as a component of NPs has been relatively limited due to the potential risk of hemorrhage. Nevertheless, heparin has been used with caution for surface-coating of NPs due to the ability to inhibit complement activation [22]. For example, heparin-coated poly(methyl methacrylate) NPs evaded reticuloendothelial system uptake and showed a longer circulation half-life than noncoated NPs [23]. Heparin-coated NPs were also used as a carrier of hemoglobin (Hb) [50,51]. Here heparin-poly(isobutylcyanoacrylate) copolymers were made into NPs, where heparin formed a hydrophilic stealth coating that spontaneously bound Hb with high efficiency [50]. The heparin-coated poly(isobutylcyanoacrylate) NPs coupled to Hb maintained the antithrombic activity of heparin and the ligand-binding capacity of Hb [50]. Heparin was also modified with a hydrophobic moiety such as deoxycholic acid (DOCA) to form self-assembled NPs [52] with the drug-loading capacity [53]. Doxorubicin loaded in the heparin-DOCA NPs induced tumor volume reduction to a greater extent than free doxorubicin, due to the extended circulation of the carrier and the antiproliferative effect of the heparin-DOCA conjugate itself [53].

The ability of heparin to control angiogenesis, tumor growth and metastasis in addition to the stealth function makes it an attractive biomaterial for the development of new nanomedicine. One of the ongoing efforts to enhance the utility of heparin in nanomedicine is to develop low-molecular-weight heparin derivatives with minimal anticoagulant effect yet high antiangiogenic activity [54].

Chitosan

Chitosan is a linear aminopolysaccharide composed of randomly distributed β -(1 $\rightarrow$ 4) linked D-glucosamine and N-acetyl-D-glucosamine units, obtained by the deacetylation of chitin from the exoskeleton of crustaceans [55]. Chitosan has been widely studied for the development of controlled drug/gene delivery systems, because of pH-sensitive water solubility, mucoadhesiveness and the ability to form a complex with nucleic acids [56]. The biological activity of chitosan varies with the physicochemical status determined by the molecular weight and degree of deacetylation [57]. The amine groups in chitosan make it uniquely suitable for covalent conjugation of anticancer drugs such as doxorubicin [58] and paclitaxel [59] for the treatment of cancer.

With a pKa value of 6.5, chitosan is typically insoluble in water at neutral pH. While this property is utilized to form self-assembled NPs [60], chitosan has also been modified in various ways to improve the water solubility in a broad range of pH, thereby enhancing its utility in physiological condition. For example, the amine groups of chitosan are partially quaternized [61] or conjugated with a sugar moiety [62]. Glycol chitosan (GC), a chitosan derivative with 2-hydroxyethylether groups in the 6-O position [63–67], low-molecular-weight chitosan (LMWC) [68] and zwitterionic chitosan [69] are also used when aqueous solubility of chitosan at neutral pH is desired.

For delivery of imaging or therapeutic agents, glycol chitosan is modified to hydrophobic moieties to form **self-assembled structures**, where hydrophilic GC forms a shell and hydrophobic moieties form a core that can encapsulate a therapeutic agent. These nanoparticulate assemblies based on hydrophobically modified GCs (HGC) showed enhanced accumulation in tumors via the EPR effect [70]. HGC made with 5 β -cholic acid has been used for the delivery of plasmid DNA (pDNA) [67], photosensitizers [71] and anticancer drugs such as paclitaxel [72], cisplatin [73] and doxorubicin [65]. HGC was also used as an imaging agent for tumor detection [70]. Here, a near-IR fluorescence dye, Cy5.5 was covalently conjugated to HGC to form approximately 150 nm NPs. The Cy5.5-labeled HGC NPs showed excellent tumor accumulation, superior to polystyrene NPs of a comparable size [70]. In another example, GC was used as a delivery vehicle of polymerized siRNA (poly-siRNA) [74]. Here, the primary amine groups of GC were partially thiolated and crosslinked via disulfide bond to stabilize the electrostatic complex with poly-siRNA. The poly-siRNA-thiolated GC complex demonstrated quick cellular uptake and efficient *in vivo* gene silencing effects in solid tumors [74]. The excellent ability of GC-based NPs to accumulate in tumors is attributed to the stability during circulation and deformability that allows for efficient extravasation at the peritumoral vasculature [70]. Moreover, GC-based NPs are shown to enter cancer cells effectively [70] via several endocytic pathways [75].

Recently, chitosan has been explored as a material for coating the NP surface [68,76–78]. Our group used LMWC (<10 kDa) to decorate the surface of poly(lactic-co-glycolic acid) (PLGA) NP. Here, a conjugate of LMWC and PLGA was formed and made into NPs, where PLGA formed a drug-encapsulating core and LMWC, a surface coating. The rationale of using LMWC as a coating material was that it would develop cationic charge at pH below its pKa value (6.5), allowing the NPs to interact with cells located in acidic environment such as hypoxic tumors [68]. Owing to the low molecular weight, LMWC was more water soluble than high-molecular-weight chitosans and formed a hydrated surface layer that was resistant to protein adsorption and phagocytic uptake [68]. The authors also reported a new water-soluble chitosan derivative, created by partial amidation of amine groups [69]. The chitosan derivative shows negative charge at neutral pH, potentially useful for coating cationic NPs.

The cellular interaction of chitosan NPs is typically explained by the electrostatic interactions between positively charged chitosan and anionic substructures on the cell membrane [56]. In addition, chitosan (19 or 31 kDa) is reported to be taken up by the renal tubular cells via **endocytosis** mediated by megalin receptor [25]. In this study, chitosan uptake by the human renal tubular cells (HK-2) was decreased in the presence of gentamycin, another ligand of the megalin receptor. They also demonstrated that the accumulation of chitosan decreased in mice treated with disodium maleate, which caused depletion of the megalin receptor in the kidney [25].

Hyaluronic acid

Hyaluronan, or hyaluronic acid (HA), is a polysaccharide composed of alternating (1→4)-β-D-glucuronic acid and (1→3)-β-N-acetyl-D-glucosamine [79]. HA is a glycosaminoglycan abundant in the body, present in the skin, lung, synovial fluid and blood [80]. Biological roles of HA vary with the molecular weight [81]. For example, high-molecular-weight HA in the extracellular matrix was shown to have an antiangiogenic effect [82]; whereas later studies using HA fragments showed that it can be a stimulator of angiogenesis [83] and endothelial differentiation [84]. Several studies report receptors of HA. CD44 is a well-known receptor of HA [85]. HARE [86], a receptor for hyaluronate-mediated motility [87], and LYVE-1 [88] are also known as receptors of HA.

Because of the biological functions and known receptors, HA has been incorporated into a wide variety of nanomedicine constructs. HA has been used for the delivery of anticancer drugs such as paclitaxel [24,26,89,90], doxorubicin [91–93] and camptothecin [94]. In addition, HA is used along with cationic liposomes and polymers to reduce cytotoxicity and their interaction with serum proteins [95]. For example, HA conjugated with polyethyleneimine (HA-PEI) was used for the delivery of siRNA and has shown effective gene silencing effect *in vitro* [96] and *in vivo* [97,98]. The presence of HA prevented particle aggregation in blood and death related to pulmonary embolism [97]. The mechanism by which the siRNA/H A-PEI complex enters cells remains controversial [96,98], but there is a possibility of receptor-mediated endocytosis, given that the siRNA-H A-PEI complex, unlike siRNA-PEI, tends to accumulate in the tissues with HA receptors [27,98]. Here, LYVE-1 was identified as a receptor for HA-conjugated NPs [27]. More efficient gene silencing was observed in B16F1 murine melanoma cells overexpressing LYVE-1 than in HEK-293 human kidney cells without HA receptors [27]. In another study, HA was used for the targeting of sinusoidal endothelial cells (SECs) of the liver via HARE [99]. Here, HA was conjugated with poly-L-lysine and complexed with pDNA. Following the tail vein injection, the pDNA-HA-poly-L-lysine complex mainly accumulated in the liver SECs and expressed a reporter gene there via HARE-mediated endocytosis [99].

HA was also shown to contribute to gene transfection by increasing extracellular stability. Previously, a ternary gene complex consisting of pDNA, disulfide cross-linked PEI and HA coating (DPH complex) was created. The ternary complex was superior to a binary complex of pDNA and cationic polymers (i.e., crosslinked PEI) in the stability under the treatment with DNase and/or heparin and the transfection efficiency in the serum-containing medium [100]. A series of experiments suggest that HA not only protects the complex from unwanted interactions with serum proteins but also helps the complex dissociate in a timely manner once internalized by cells [100]. It is suggested that the intracellular decomplexation of the HA-containing complex facilitates the access of transcription factors to pDNA and subsequent gene expression processes [100,101].

Chondroitin sulfate

Chondroitin sulfate (CS) is a negatively charged glycosaminoglycan consisting of two alternating monosaccharides (*N*-acetylgalactosamine and glucuronic acid). CS is present on the cell surface and in the extracellular matrix [102], and covalently bound to proteins to form a proteoglycans [103]. Due to the good biocompatibility and hydrophilicity, several nanocarriers have been developed based on CS.

Since CS is highly hydrophilic, it is modified with additional moieties such as polylactide [103,104], acetyl groups [105] or methacrylate [106], which enable the formation of self-assembled nanocarriers and the loading of therapeutic agents. Alternatively, CS is used to coat a DNA–PEI complex to shield the cationic charge [107,108]. A ternary complex consisting of DNA, PEI and CS showed greater *in vitro* gene transfection efficiency and tumor accumulation than the DNA–PEI complex [108]. A ternary complex consisting of CS, PEI and DNA encoding mGM-CSF also inhibited the growth of intraperitoneal and subcutaneous tumors in a syngeneic mouse model to a greater extent than a binary complex of PEI and mGM-CSF DNA or another ternary complex using high-molecular-weight HA instead of CS [107].

The improvement of gene transfection and tumor-targeting effect by CS was attributed to the high expression of CD44, one of its receptors, on tumor cells [109]. Kurosaki *et al.* compared the effects of various polysaccharides as coating materials for pDNA–PEI complex and found that the CS-coated complex entered cells most effectively among the tested polysaccharide-based complexes [110]. Given that the uptake of the pDNA–PEI–CS complex was blocked by free CS added to the culture medium in a dose-dependent manner, the uptake of the CS-based ternary complex is likely to be through receptor-mediated endocytosis [110].

In addition, CS coating contributed to the safety of gene complexes. CS was added to a polymeric complex based on a polyaspartamide derivative to improve the safety and transfection efficiency [111]. As compared with a binary complex lacking CS, the ternary complex induced lower levels of lactate dehydrogenase, a marker of tissue damage, and pro-inflammatory cytokines such as TNF- α and COX-2 in lung tissues after gene delivery via intratracheal administration [111]. Serum creatine phosphokinase level, another indicator of tissue damage, measured after hydrodynamic gene introduction into skeletal muscle was also lower in the CS added group [111]. The protective effect of CS is attributable to neutralization of excessive positive charges, which cause cell-membrane damage when left unmasked [111].

Future perspective

Main advantages of polysaccharides are well-established biocompatibility, availability and abundant functional groups amenable to chemical modifications. Many research groups are exploring these advantages to improve the effectiveness of nanomedicines. However, several challenges remain to be overcome. First, most polysaccharides are of natural origin, and there is a high degree of variability with respect to the molecular weight and structure depending on the sources. Since these properties critically influence the biological activities of polysaccharides, alternative methods to produce polysaccharides with consistent properties need to be established for further advancement of polysaccharide-based nanomedicines. Second, depending on the origin, a polysaccharide may contain biologically active contaminants such as endotoxins and pathogens that may counteract the desired effect of the polysaccharide. Standardized procedures to purify polysaccharides are urgently needed. Third, the exact mechanisms of prominent biological actions of polysaccharides remain to be identified. It is not unusual to observe apparently contradicting activities of the

'same' polysaccharide. A subtle difference in molecular weight, degree of branching, or the arrangement of monomers can result in significant differences in their biological effects. Moreover, the biological effects and fates of excess polysaccharides and degradation products are not entirely clear. An understanding of the mechanism of action is a prerequisite to successful utilization of a polysaccharide in nanomedicine development.

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Key Terms

Reticuloendothelial system	Special immune system primarily consisting of monocytes and macrophages located in reticular connective tissue such as lymph nodes and the spleen. The Kupffer cells of the liver and tissue histiocytes are also part of the reticuloendothelial system.
Opsonization	Rendering of bacteria and other foreign substances subject to phagocytosis by opsonins such as antibodies and complements.
Stealth coating	Covering of the nanoparticle surface with an electrically neutral hydrophilic polymer. The hydrated surface layer prevents protein adsorption and recognition by immune cells.
Anticoagulation	Prevention of blood clotting. Heparin is a representative anticoagulant. Anticoagulants are used in medical conditions involving excessive blood clotting, such as deep vein thrombosis, pulmonary embolism, myocardial infarction and stroke.
Angiogenesis	Physiological or pathological process involving the growth of new blood vessels. Although a normal process in growth, development and wound healing, it is also a crucial process in the growth of tumors.
Self-assembled structures	Ordered arrangements of amphiphilic materials, which not only maintain molecular properties of individual building blocks, but also have novel properties that can perform specific functions.
Endocytosis	Process by which cells take up molecules or nanoparticles. Examples of endocytosis pathways are clathrin-mediated endocytosis, caveolae-mediated endocytosis, macropinocytosis and phagocytosis.

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Executive summary

Use of polysaccharides in nanomedicine

- Naturally occurring polysaccharides, such as dextran, heparin, chitosan, hyaluronic acid and chondroitin sulfate are widely used for surface modification of nanomedicines.
- These polysaccharides can reduce opsonization and complement activation due to nanomedicines in the blood and, thus, increase their circulation half-lives.
- Some polysaccharides can function as a ligand and enhance the cellular uptake of nanomedicines via receptor-mediated endocytosis.
- Advantages of polysaccharides include biocompatibility, cost-effectiveness and well-established modification schemes.

Remaining challenges

- A high degree of variability, potential risk of bioactive contamination and insufficient mechanistic understanding of the biological actions remain as challenges.

Figure 1.
Polysaccharides frequently used for surface modifications of nanomedicines.

Figure 2. Various types of polysaccharide-based nanoparticles

(A) Polysaccharide-forming layers on the nanoparticle surfaces via electrostatic interactions or physical adherence. **(B)** Self-assembly of a hydrophilic polysaccharide with hydrophobic grafts. **(C)** Nanoparticles made of conjugates of polysaccharides and synthetic polymers.