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Carbohydrate-based nanomaterials for biomedical applications

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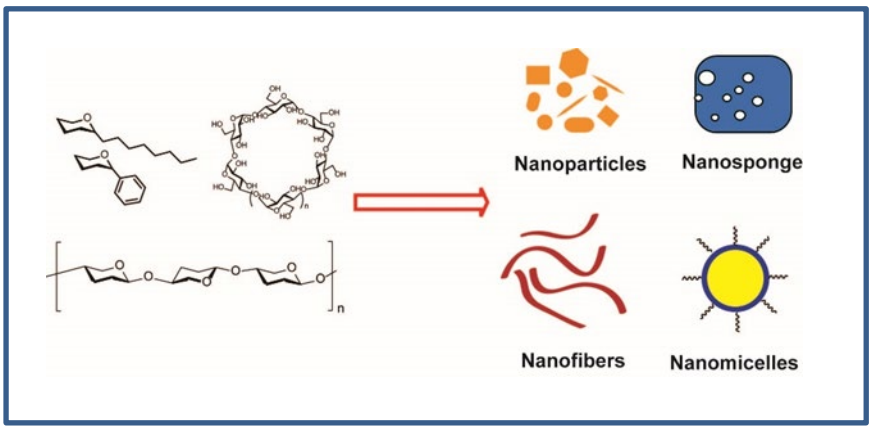

Carbohydrates aggregate to form materials with different shapes and tunable properties. These compounds are valuable for biomedical applications, including drug delivery and tissue engineering.

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Abstract

Carbohydrates are abundant biomolecules, with a strong tendency to form supramolecular networks. A host of carbohydrate-based nanomaterials have been exploited for biomedical applications. These structures are based on simple mono- or disaccharides, as well as on complex, polymeric systems. Chemical modifications serve to tune the shapes and properties of these materials. In particular, carbohydrate-based nanoparticles and nanogels were used for drug delivery, imaging, and tissue engineering applications. Due to the reversible nature of the assembly, often based on a combination of hydrogen bonding and hydrophobic interactions, carbohydrate-based materials are valuable substrates for the creations of responsive systems. Herein, we review the current research on carbohydrate-based nanomaterials, with a particular focus on carbohydrate assembly. We will discuss how these systems are formed and how their properties are tuned. Particular emphasis will be placed on the use of carbohydrates for biomedical applications.

Introduction

Carbohydrates comprise more than 80% of biomass, making them the most abundant class of biopolymers on earth. They mainly serve energy storage and structural functions. Recently, the regulatory role of carbohydrates in several biological processes has become evident (A. Varki; R. Cummings; J. Esko; H. Freeze; P. Stanley; G. Hart; P.H. Seeberger, 2017). Cell differentiation, proliferation and adhesion, inflammation and immune responses are connected to carbohydrate-carbohydrate (CCIs) (Rojo, Morales, & Penadés, 2002) and carbohydrate-protein (CPIs) (Y. C. Lee & Lee, 1995) interactions. These interactions are weak, often in the micro to millimolar range, so nature makes use of multiple weak interactions to circumvent this issue (multivalency). The concept of multivalency has been exploited by synthetic chemists in order to mimic nature (Fasting et al., 2012). Several nanostructures, coated with multiple copies of the same carbohydrate ligand, permitted to increase the CPI and CCI strength (Delbianco, Bharate, Varela-Aramburu, & Seeberger, 2016; Jiménez Blanco, Ortiz Mellet, & García Fernández, 2013). Enhanced water solubility and stability are also observed. Glycosylated scaffolds, such as polymers, nanoparticles, and surfaces, are potential drug delivery systems, vaccines, and therapeutics that have been reviewed extensively (Chabre & Roy, 2013; Delbianco et al., 2016; Kiessling & Grim, 2013; Marradi, Chiodo, García, & Penadés, 2013; Sansone & Casnati, 2013). The tendency of carbohydrates to form supramolecular networks, via a multitude of hydrogen bonds, guided the development of self-assembling systems (Delbianco et al., 2016).

CCIs and CPIs are generally regulated by long complex polysaccharides. Nevertheless, for simplicity, most glycosylated-materials are based on a synthetic scaffold functionalized with multiple copies of simple mono- or oligosaccharides. Such molecules can be prepared by chemical synthesis and/or

enzymatic methods, obtaining well-defined structures (Kadokawa, 2011; Panza, Pistorio, Stine, & Demchenko, 2018; Pardo-Vargas, Delbianco, & Seeberger, 2018); unnatural structures are also accessible through chemical modifications. As an alternative to synthetic compounds, polysaccharides extracted from natural sources offer a valuable substrate for the formation of materials (Garcia-Vaquero, Rajauria, O'Doherty, & Sweeney, 2017; Ruthes, Smiderle, & Iacomini, 2015). Their abundance, biocompatibility, and tendency to form stable supramolecular networks are extremely appealing features for the creation of nanomaterials, like nanoparticles or gels (Figure 1). Additionally, these polymers could be easily functionalized to improve solubility, stability, encapsulation and responsiveness (Cumpstey, 2013; Fox, Li, Xu, & Edgar, 2011; Jedvert & Heinze, 2017). Both natural and chemically modified structures found several applications in imaging (Swierczewska, Han, Kim, Park, & Lee, 2016; Wondraczek, Kotiaho, Fardim, & Heinze, 2011), drug delivery (Gopinath, Saravanan, Al-Maleki, Ramesh, & Vadivelu, 2018; Z. Liu, Jiao, Wang, Zhou, & Zhang, 2008), and tissue engineering (J. Hu, Seeberger, & Yin, 2016). Nevertheless, extracted polysaccharides exist as polydisperse samples with multiple lengths and branching, making the analysis, reproducibility and quality control of such materials very difficult. Due to the single chain flexibility, a detailed 3D investigation, as well as a defined structure-function correlation, is still lacking. In addition, chemical modifications, that serve to tune the polysaccharides properties, suffer from low regioselectivity, increasing the sample polydispersity even further.

Despite the challenges, carbohydrates remain an exciting substrate for biomaterial applications, due to their biological relevance and tendency to form supramolecular networks. Here, we review the recent progress in the field of carbohydrate-based nanomaterials. We will focus on supramolecular carbohydrate-based assemblies, in which the supramolecular aggregation is guided and controlled by the carbohydrate part (glycomaterials). Pre-assembled materials, further functionalized via glycosylation (glycosylated materials), will not be discussed in this review. We will start from simple architectures based on carbohydrate monomers, continuing to more complex polysaccharides-based materials. Particular focus will be given to the assemblies used for biomedical applications.

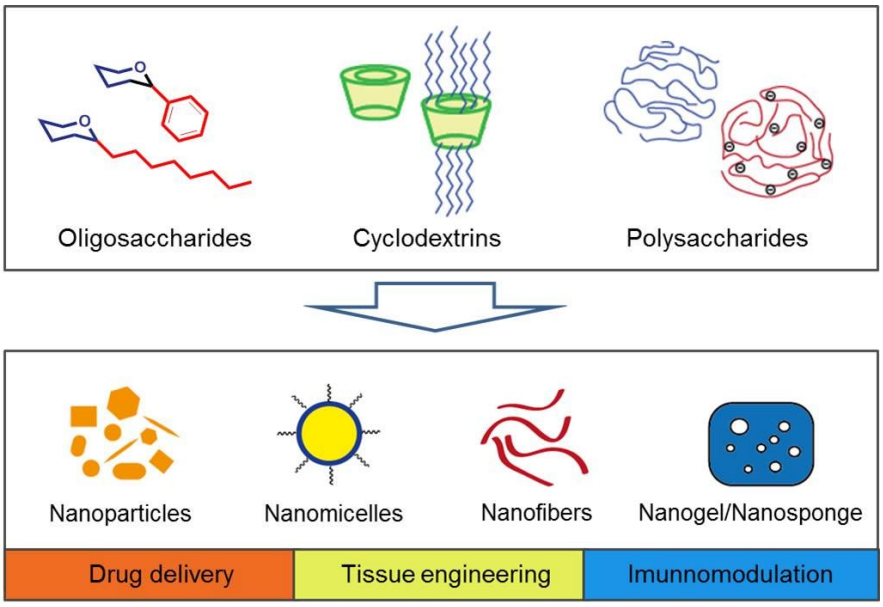

Figure 1: Schematic representation of the different classes of carbohydrates used to form nanomaterials for biomedical applications.

OLIGOSACCHARIDES

Monomers and Dimers

Mono- and oligosaccharides have been modified extensively to give glycoamphiphiles and generate diverse morphologies like micelles, vesicles, and fibers (Figure 2). Non-covalent interactions such as hydrogen bonds, hydrophobic, and metal-ligand interactions promote the formation of the assembly. Moreover, several examples of dissociation of the assembly in response to external stimuli, such as heat, light, and ultrasound, have been reported. This behavior is particularly important for drug delivery systems, where the responsive release can be exploited to minimize drug side effects. As an example, lactose-conjugated dendrimers with a photo-responsive hydrophobic part can selectively release doxorubicin in cancel cells, upon NIR or UV irradiation (L. Sun, Ma, Dong, Zhu, & Zhu, 2012). In addition, the amphiphilic nature of most sugar materials permits the encapsulation of both hydrophilic and hydrophobic molecules. Water-soluble compounds like enzymes, plasmid DNA, and genes as well as water-insoluble dyes can be delivered upon encapsulation into sugar micelles and vesicles (**1-3**) (Gour, Purohit, Verma, Puri, & Ganesh, 2009; Ryu, Lee, Lim, & Lee, 2007; Salim et al., 2015) .

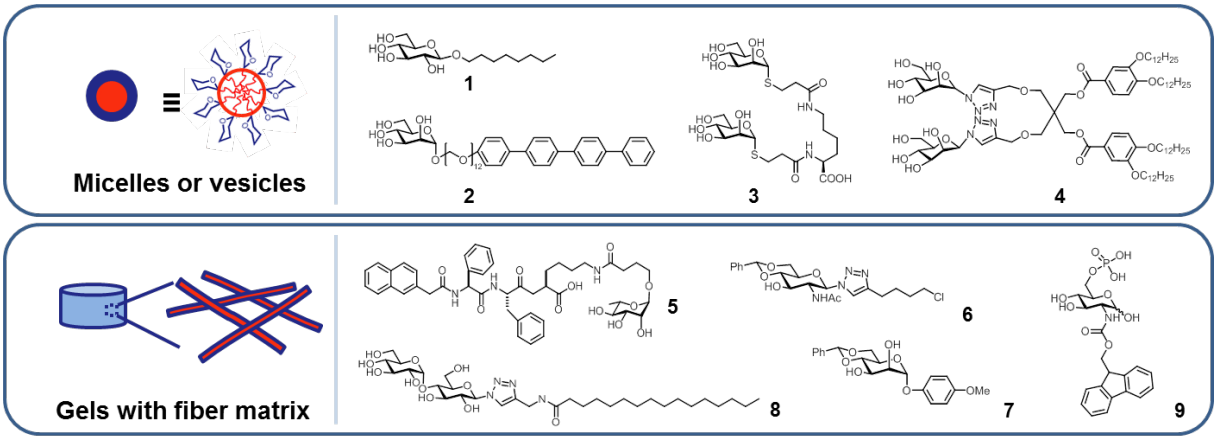

Figure 2: Chemical structures and supramolecular assembly of monosaccharides amphiphiles.

An important role of mono- and oligosaccharides is cell recognition (Lis & Sharon, 1998). This process is based on the interaction between carbohydrate binding proteins (i.e. lectins) and carbohydrates on the cell surface and is often involved in the primary stage of pathogen infection. Sugar-assemblies have been exploited to target lectins and inhibit bacterial infections (**2-4**) (B. S. Kim, Yang, Ryu, Yoo, & Lee, 2005; D. W. Lee, Kim, Park, Huang, & Lee, 2012; Lim et al., 2007; Percec et al., 2013; Ryu et al., 2007; S. Zhang et al., 2015; S. Zhang et al., 2014). Structure and concentration of the sugar amphiphile regulates the morphology of the supramolecular complexes. At the same time, the density of the exposed sugars influence the cell recognition ability (Y. Liu, Zhang, et al., 2016). Glycoclusters based on metal-ligand interactions offer an interesting alternative. Pipyridyl-glycoclusters functionalized with the Tn-antigen (α-GalNAc-OR) were used for the formation of copper(II) complexes with enhanced binding to *Vicia villo* lectin (R. Roy & Kim, 2003). Similarly, a catechol-functionalized iron(III) glycodendrimer better targeted *E. coli* ORN78 and was used as an iron delivery carrier (Yadav & Kikkeri, 2012). Saccharide-coated $M_{12}L_{24}$ complexes based on Pd(II) (Y. Liu, Zhang, et al., 2016) showed potential in Alzheimer diagnosis (Sato et al., 2015; Yan et al., 2017). The use of sugar nanostructures for immunomodulation was first reported in 2014 as the assembled nanofibrils encapsulate antigens and interact with human antibodies. In contrast to monomeric L-rhamnose, which increased antibody response, the nanofibrils base on **5** reduced the antibody response to the antigen phycoerythrin,

suggesting that this system may be a synthetic immunomodulatory material (Zhao et al., 2014). Recently, glycopeptide nanostructures have been proposed for regenerative therapy (S. S. Lee, Fyrner, et al., 2017). Nanofibers composed of a glycopeptide bearing a trisulfated monosaccharide can mimic heparan sulfate, a polysaccharide that binds growth factors that are in turn responsible for cell proliferation and differentiation related with bone formation.

Modified mono- and disaccharides have been extensively used as low molecular weight gelators (LMWGs). Most sugar gelators are conjugated to hydrophobic moieties (**6,7,8**), such as aliphatic chains or aromatic groups (A. Chen, Okafor, Garcia, & Wang, 2018; Clemente, Romero, Serrano, Fitremann, & Oriol, 2012; Guan et al., 2016; Krishnan, Raghu, Mukherjee, & Sureshan, 2016; Mathiselvam, Loganathan, & Varghese, 2013; Mitra, Sarkar, & Mukhopadhyay, 2017; Pathak, Halder, Dhara, & Yadav, 2017). These sugar-derived supramolecular structures can encapsulate hydrophobic drugs to increase drug solubility and serve as scaffolds for biomedical applications. Moreover, 3D gel matrixes from sugar gelators were exploited as a tissue engineering scaffold and for cell proliferation (Ustun Yaylaci et al., 2016). Highly elastic hydrogels, suitable for adhesion and proliferation of isolated stem cells, were obtained from a glucosyl-nucleoside bola-amphiphiles (Latxague et al., 2015). Responsive gels, that form or degrade upon an external stimulus, were developed as well. Gelation of a phosphate containing carbohydrate amphiphile **9** induced by alkaline phosphatase produced by osteosarcoma cells can suppress metastasis by blocking metabolite exchange between cells (Pires et al., 2015). A glucose-conjugated prodrug assembled into a thermo-responsive gel and was employed as a biocompatible drug with reduced inflammatory effect (Xiong et al., 2018).

Supramolecular structures formed from mono- and oligosaccharides proved to be important substrates for biomedical applications, such as bacterial infection inhibition and bone regeneration. The majority of these systems require several modifications with bulky proteins or lipid units. Moreover, most studies were limited to the use of mono- and disaccharides. With the development of synthetic techniques that allow for quick access to longer oligosaccharides, new glycomaterials, requiring less functionalization, can be envisioned (Hahm et al., 2017; Panza et al., 2018; Pardo-Vargas et al., 2018; Wen et al., 2018).

Cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides constituted of glucopyranose units linked α-(1,4), commonly produced during the degradation of starch. The most common CDs are α-, β-, and γ-CDs, consisting of six, seven, and eight glucose units. Because of their cavity, CDs can form unique inclusion complexes with specific molecules, and further assemble into supramolecular structures (Crini, 2014). Hence, they are potential structural units to build nanomaterials as discussed in several excellent reviews (Bellia et al., 2009; Delbianco et al., 2016; Q. D. Hu, Tang, & Chu, 2014; Martinez, Ortiz Mellet, & Garcia Fernandez, 2013; Schmidt & Barner-Kowollik, 2017; Wenz, 1994). Here, we describe recent work related to structural properties and biomedical applications of nanomaterials assembled from CD structures.

CDs usually assemble in three different packing patterns: cage, channel, and layer type superstructures (Figure 3) (Harata, 1998). In the cage pattern, the cavity is sealed by another CD. In the channel pattern, the CD molecules arrange regularly through hydrogen bonds to form linear structures, so the cavities stack together to form the channel. The layer type CDs are arranged in parallel, however, the cavities are shielded due to a half-molecule shift between the layers. These systems can further assemble into a variety of geometries, such as particles and fibers (CD-based materials).

CD-based materials have been applied in the food and pharmaceutical industries since the 1980s (Crini, 2014) and show great potential for biomedical applications. Different methods to prepare CD-based materials in aqueous environment exist (González-Gaitano et al., 2002; Shigemitsu & Kida, 2018; Szente, Szejtli, & Kis, 1998; A. Wu, Shen, & He, 2006a, 2006b). CDs and their inclusion complex nanofibers were prepared by electrospinning (Celebioglu & Uyar, 2012, 2013a, 2013b; Kayaci & Uyar, 2012; Uyar, Balan, Toppare, & Besenbacher, 2009; Uyar & Besenbacher, 2009; Uyar, Nur, Hacaloglu, & Besenbacher, 2009). Guest-free channels can be prepared by a solvent switch from α- and γ-CD (Rusa et al., 2002; Uyar, Hunt, Gracz, & Tonelli, 2006), whereas cubic crystals can be obtained from γ-CD (Kida, Marui, Miyawaki, Kato, & Akashi, 2009; Marui, Kida, & Akashi, 2009). CD drug delivery systems, allow for encapsulation of small drug molecules as well as large biomolecules (Challa, Ahuja, Ali, & Khar, 2005; Davis & Brewster, 2004; Del Valle, 2004; Rajewski & Stella, 1996; Stella & Rajewski, 1997). The antidepressants, dothiepin (DOT) and doxepin (DOX) formed 1:2 inclusion nanostructures with α- and β-CDs and assemble into sphere and agglomerated structures (Rajendiran, Sankaranarayanan, & Saravanan, 2014). More complicated systems, involving the ternary complex “Guest 2/(Guest 1/γ-CD)” permitted to load two different drugs at the same time; the first guest is located in the CD cavity, and the second guest is incorporated into the intermolecular spaces between CD channels (N. Liu, Higashi, Ueda, & Moribe, 2017).

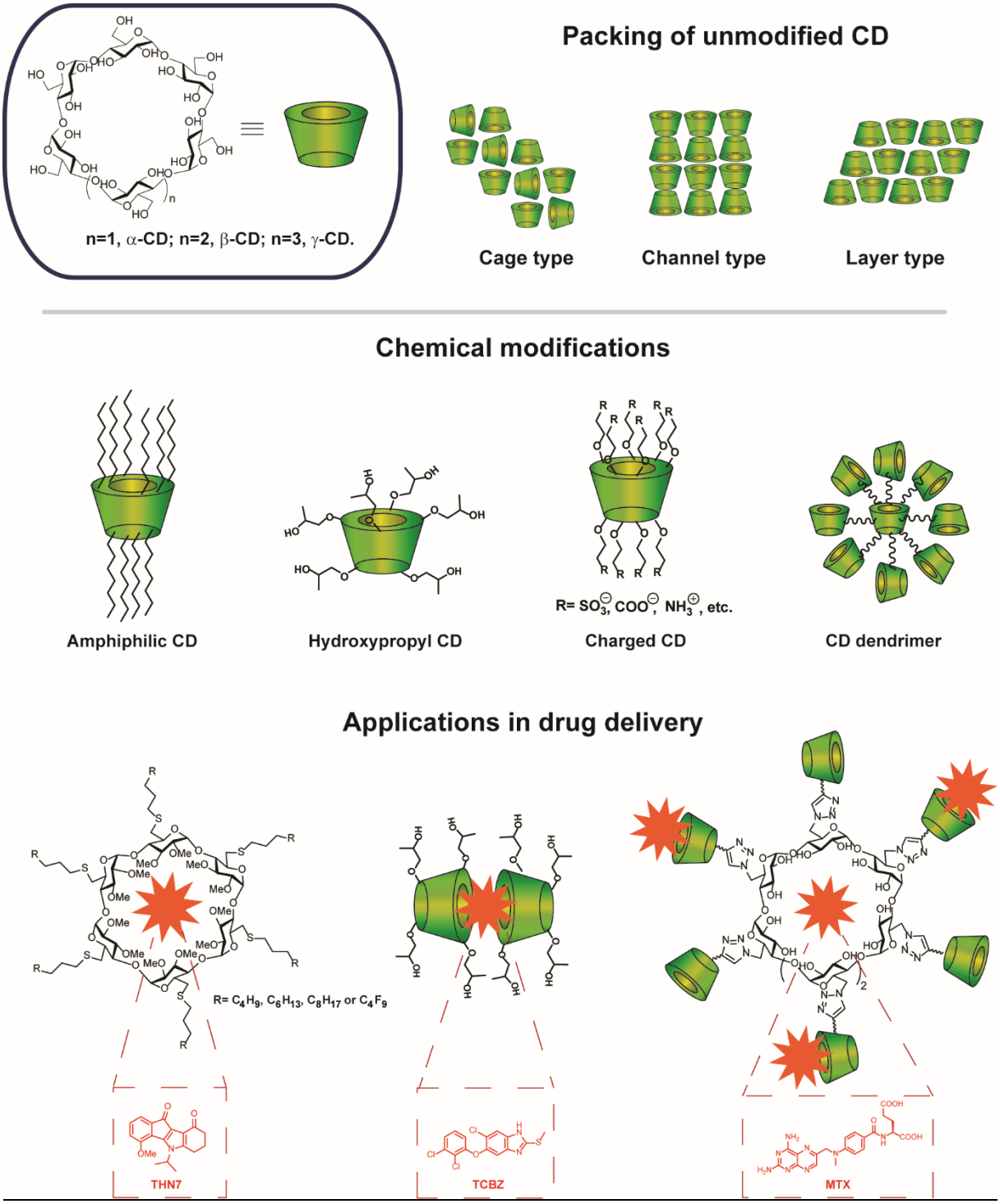

Figure 3: CD packing patterns, common CD modifications, and examples of CD systems for drug delivery applications.

Chemical modifications greatly expand pharmaceutical applications of CDs. Amphiphilic CDs engage in stronger interactions with hydrophobic drugs and can self-assemble into a variety of nanostructures, in aqueous systems. The hydrophobic part of these assemblies enters into strong interactions with biological membranes, thus increasing cellular uptake (Varan, Varan, Erdoğar, Hıncal, & Bilensoy, 2017). α-CD were modified at the 6 position with diffident kinds of fluorinated and hydrocarbonated amphiphilic chains to encapsulate 4-methoxy-5-isopropyl-5, 6, 7, 8-tetrahydroindeno [1, 2-b] indole-9, 10-dione (THN7), an inhibitor of casein kinase 2, and form nanoparticles of around 100 nm diameter size (Figure 3)(Nacereddine et al., 2018).

2-Hydroxypropyl cyclodextrins (HP-CDs) are widely used for drug delivery. Upon random methylation, β-CD and HP-β-CD served as carriers for drug nebulization (Evrard et al., 2004). An aqueous cyclosporin A eye drop was developed based on both natural CDs and HP-CDs (Jóhannsdóttir, Jansook, Stefánsson, & Loftsson, 2015). HP-β-CD/budesonide microparticles were spray-dried to treat lung inflammation (Dufour et al., 2015). The inclusion complex between triclabendazole (TCBZ) and HP-β-CD or methyl-β-cyclodextrin (Me-β-CD) can form different superstructures, that are highly soluble for drug delivery applications (Figure 3) (Real, Leonardi, Williams, Repka, & Salomon, 2018). The advantage of HP-CDs was illustrated for the CD/Griseofulvin (GF) complex. Although β-CDs and Me-β-CDs were as effective in stabilizing the drug suspensions and reducing the size of drug nanoparticles, HP-β-CD showed the highest efficacy (Meng, Yang, Keyvan, Michniak-Kohn, & Mitra, 2012).

Hydrophilic CD derivatives, bearing charged functional groups, were developed as an alternative to amphiphilic CDs. Non-ionic amphiphilic CD and polycationic amphiphilic CD functionalized with amino groups were used as nanocarrier for paclitaxel. The strong positive charge helped to increase the loading capacity of the nanoparticles (Varan, Benito, Mellet, & Bilensoy, 2017). Moreover, charged CDs are interesting substrates to prepare nanosponges, permitting high loading and better delivery for a wide variety of drugs (Selvamuthukumar, Anandam, Krishnamoorthy, & Rajappan, 2012). The negatively charged sulfo-butylether-β-cyclodextrin (SBE-β-CD) was crosslinked by epichlorohydrine and form a nanosponge, used as deliver system for repaglinide (Olteanu, Aramă, Radu, Mihăescu, & Monciu, 2014). Carbonate and carboxylate functionalized cyclodextrins also assembled into nanosponges for acyclovir encapsulation (Lembo et al., 2013). Moreover, a glutathione (GSH) responsive nanosponge was developed by crosslinking β-CD, pyromellitic dianhydride and 2-hydroxyethyl disulfide, with potential for doxorubicin encapsulation. The drug release profile was accelerated in the presence of increasing amounts of glutathione (GSH) (Trotta et al., 2016).

New modifications are studied to produce novel CD materials with improved performance. Nanocarriers formed by epichlorohydrine crosslinked CD polymers can significantly enhance the solubility of sorafenib in water (Giglio et al., 2018). Multi-responsive CD vesicles, consisting of (*N*, *N'*-bis(ferrocenylmethylene)-diaminohexane) and (γ-hydroxybutyric-β-cyclodextrin, γ-HB-β-CD), showed redox-responsive behavior. The same system is pH responsive and reacts to the presence of metal ions such as Cu^{2+} (Huacheng Zhang et al., 2010). Dendrimers based on β-CD and ethylenediamine accommodate naproxen and naltrexone in gaps of the dendritic structure as well as in the hydrophobic cavities of the CDs (Martinez et al., 2013). A similar β-CD dendrimer provided a controlled drug delivery system for methotrexate (MTX) for cancer treatment (Figure 3) (Toomari, Namazi, & Akbar, 2015). Amphiphilic β-CD nanoparticles were developed as nanocarriers for doxorubicin (DOX). The assemblies were further functionalized with mannose, to facilitate the cancer cell targeted drug delivery. The system showed good tumor growth inhibition in the murine xenograft tumor models (Ye et al., 2016)

Several nanomaterials were prepared from different CD units and applied to the development of drug delivery systems, nevertheless, structure-function relationship have yet to be established. A better understanding of the relationships between the chemical modification, preparation, and structural property of CD materials, will help the design and creation of new CD nanostructures for the specific needs.

POLYSACCHARIDES

Neutral polysaccharides

Cellulose

Cellulose is the most abundant biopolymer on earth and a major structural component in plants, algae, fungi, and bacteria (Klemm, Heublein, Fink, & Bohn, 2005). D-glycopyranose monomers are connected to each other with β-(1,4)-glycosidic linkage forming elementary fibrils (protofibrils). Cellulose microfibrils arise from a large number of inter- and intramolecular interactions of the protofibrils, ensuring high mechanical strength, durability, and water-insolubility. These features allow for the use of cellulose in the paper, textile, filter, and building material industry (Moon, Martini, Nairn, Simonsen, & Youngblood, 2011). Recently, nanocellulose (NC) has gained attention as material (Thomas et al., 2018). Three main classes of NC exist: cellulose nanocrystals (CNCs), nanofibrillated cellulose (NFC), and bacterial nanocellulose (BNC). NC can be extracted from various biosources and it is easily chemically or physically modified (Kargarzadeh et al., 2018). Like other nanomaterials, NC shows a high surface to volume ratio and improved solubility compared to natural cellulose. Here, we will focus on materials obtained by self-assembly of substituted cellulose, since NC has been extensively reviewed (Amalraj, Gopi, Thomas, & Haponiuk, 2018; Jorfi & Foster, 2015; Picheth et al., 2017; Seabra, Bernardes, Fávaro, Paula, & Durán, 2017).

The limited water solubility of cellulose is a critical obstacle for biomedical applications. For a better usage of cellulose in drug delivery, wound healing, and tissue/regenerative engineering, structural modifications have been introduced to decrease inter- and intramolecular hydrogen bonding (D. Roy, Semsarilar, Guthrie, & Perrier, 2009). The cellulose backbone, rich in hydroxyl groups, can be esterified and etherified. Due to the poor solubility of cellulose in common solvents, ionic liquids, such as 1-n-butyl-3-methylimidazolium chloride (BmimCl) and 1-n-alkyl-3-metylimidazolium chloride (AmimCl), are generally employed. Cellulose acetate (CA), ethylcellulose (EC), hydroxypropylcellulose (HPC), and carbohymethylcellulose (CMC) are the most common cellulose derivatives (Figure 4), with improved water solubility. Hydrophobic segments, like poly(L-lactic acid), have been grafted onto the cellulose backbone to give rise to amphiphilic copolymers (Dai & Si, 2017; Guo, Wang, Shu, Shen, & Sun, 2012).

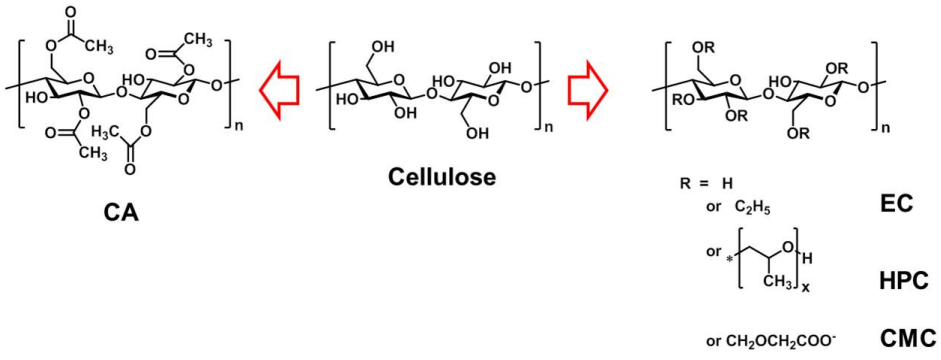

Figure 4: Chemical structure of cellulose and its most common derivatives.

CA is the acetate ester of cellulose, obtained from the reaction of cellulose with acetic anhydride and acetic acid in the presence of sulfuric acid. The solubility of CA is influenced by the degree of

acetylation.(Fischer et al., 2008) Earlier studies on CA mainly focused on the formation of cellulose beads, resulting in a commercially available system for medical applications (Milovanovic et al., 2016). CA beads are prepared *via* oil-in-water emulsion/solvent evaporation, offering high mechanical strength, suitable for bone tissue engineering (Kumbar et al., 2011). Cellulose acetate phthalate (CAPh) successfully generated CAPh-dye beads by encapsulation, which were used as visually readable labels in lateral flow immunoassays (Schulze et al., 2016). Since the development of electrospinning for nanobiotechnology, improving drug encapsulation efficiency and easing fabrication (Samadian, Mobasheri, Hasanpour, & Majid, 2017), the recent research on CA focuses on electrospun fibers (Khoshnevisan et al., 2018; Sharaf & El-Naggar, 2018). Chlorohexidine-containing CA electrospun nanofibers showed antibacterial activity against oral pathogens, permitting a release of the drug over 90 days (De Carvalho et al., 2017). Dexamethasone-loaded electrospun CA scaffolds provided a good environment for cell growing and proliferation, suggesting the possibility to reduce implant-associated acute inflammations and impede implant failure (Tsiapla et al., 2018). Functionalized stimuli-responsive CA were also developed. A boronic acid ligand-functionalized CA nanofiber, which is able to selectively bind and release glycoproteins (e.g. ovalbumin) depending on the pH, was used in diagnostics (Dong et al., 2018).

Short aliphatic moieties were used to functionalize the cellulose backbone to give EC, HPC, and other derivatives, that are readily soluble in common organic solvents. The hydrophobic modification allows for the self-assembly of the cellulose derivatives in aqueous solution and encapsulation of hydrophobic dyes (Xiaohui Wang, Guo, Li, Chen, & Sun, 2012). In addition, EC can form gels by the solvent-exchange method. Antimicrobial agents were encapsulated in such gels providing a simple syringe injectable drug for periodontitis (Phaechamud & Mahadlek, 2015). Atom transfer radical polymerization (ATRP) is the most widely used technique for further modification of cellulose derivatives (Kang, Liu, & Huang, 2015; D. Roy et al., 2009). Generally, the cellulose hydroxyl groups are modified with 2-bromoisobutyryl bromide to initiate the polymerization reaction. Light sensitive triblock copolymers were successfully obtained by ATRP of EC and spiropyran ether methacrylate (SPMA). The SPMA light responsive moieties permitted a wavelength dependent controlled drug release (B. Wang, Chen, Yang, Yang, & Liu, 2014). An alternative system uses pendant disulfide linkages to form a HPC crosslinked structure with excellent colloidal stability and selective drug release behavior, in the presence of a reducing agent (Rahimian, Wen, & Oh, 2015).

The introduction of negative charges onto the cellulose backbone, not only affects the supramolecular structure formation, but also the bioactivity of the resulting aggregates. CMC is the most common charged cellulose derivative, bearing negative carboxymethyl groups. The carboxylic groups make cellulose soluble in water and chemically reactive. Due to its negative nature, CMC can generate supramolecular structure with positive charged polymers or metals (Figure 5) (Agarwal et al., 2015; Barkhordari, Yadollahi, & Namazi, 2014; Upadhyaya, Singh, Agarwal, Pandey, et al., 2014). CMC and quaternary ammonium substituted cellulose formed a ampholytic hydrogel responsive to pH and salt concentration, which makes a good candidate for tissue engineering (Chang, He, Zhou, & Zhang, 2011). Similarly, a mixture of lysozyme (Ly), a globular positive charged protein, and CMC is a promising drug delivery carrier (Zhenshun Li, Wang, et al., 2017; K. Zhu et al., 2013). This system can incorporate quantum dots for cell imaging (Zhenshun Li et al., 2015). Hydroxyl groups of CMC and acid-functionalized multi-walled carbon nanotube (MWCNT) generated a hybrid nanocomposite hydrogel via strong hydrogen bonding between the two components, leading to a sustained release of diclofenac sodium (Mandal, Das, Rameshbabu, Dhara, & Pal, 2016). Following the same idea, a CMC/graphene oxide (GO) hydrogel was obtained. This gel was converted into spherical beads by

addition of iron ions (Rasoulzadeh & Namazi, 2017). Even simple organic molecules, like citric acid, can crosslink CMC and form hydrogels with enhanced mechanical properties, and suitable for topical chemotherapy (Capanema et al., 2018).

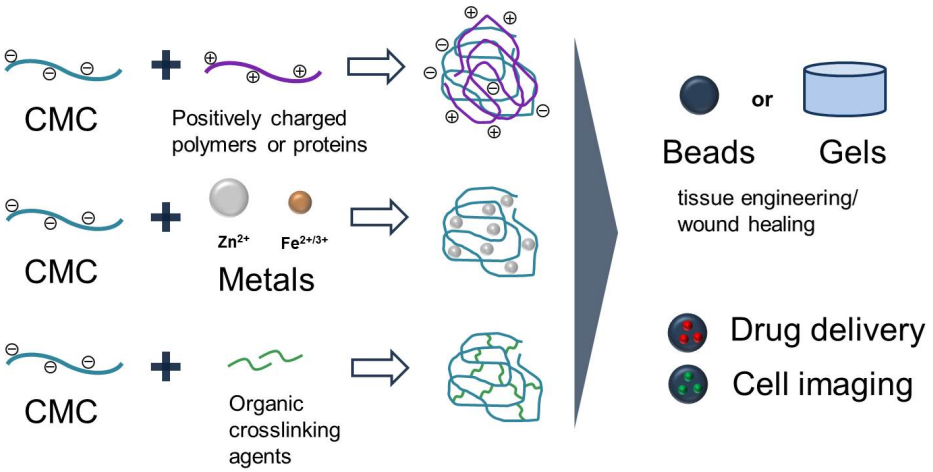

Figure 5: Co-assembly of CMC to form nanomaterials.

CMC has been modified in many ways to tune its properties for biomedical applications. Acetylated CMC improved drug coupling efficiency and colloidal stability (Hoang et al., 2015). Mucoadhesive properties were obtained by conjugation of L-cysteines to the CMC backbone (Laffleur & Messirek, 2016). Tumor targeting was tackled with covalent conjugation of cancer drugs and folate ligands to CMC (Dai et al., 2015). β -CD grafted CMC gels showed more effective tetracyclin-loading efficiency as compare to normal CMC gel (Jeong et al., 2018). Insertion of the photo-active cinnamic acid hydrazide moieties into the oxidized dialdehyde CMC core generated an adjustable photo-crosslinked hydrogel with improved mechanical properties (Monier, Abdel-Latif, & Ji, 2016). Crosslinking performed by microwaved assisted radical transfer increased the hydrogel stability and improved the sustained drug release (Sood, Gupta, Agarwal, Dev, & Pathania, 2017).

Dextran

Dextran, a glucose homopolysaccharide based on an α-(1,6) backbone with α-(1,2), α-(1,3), or α-(1,4) side chains, is a highly water-soluble bacterial glycan with good biocompatibility and biodegradability with the tendency to form nanomaterials, and widely used in the pharmaceutical industry (Naessens, Cerdobbel, Soetaert, & Vandamme, 2005). Many reviews summarize the use of dextran for drug delivery and tissue engineering (Bisht & Maitra, 2009; Debele, Mekuria, & Tsai, 2016; Mehvar, 2000; Miao, Wang, Zeng, Liu, & Chen, 2018; Mizrahy & Peer, 2012; Mokhtarzadeh, Alibakhshi, Hejazi, Omidi, & Dolatabadi, 2016; G. Sun & Mao, 2012; Van Tomme & Hennink, 2007). We will focus on the recent advances on assemblies and nanostructures based on dextran and its chemical derivatives.

Several dextran aggregates, of different size and shape, were produced and used for drug encapsulation. Microcapsules based on natural dextran with different molecular weight (10 kDa - 500 kDa) were prepared by spray drying. The drug budesonide was co-fibred at different drug-to-dextran ratios, showing that a 1:10 drug-to-polymer ratio can successfully deliver the drug to the colon to treat acetic acid-induced colitis (Varshosaz et al., 2011). Hybrid dextran nanoparticles with core-shell structure were developed to carry zidovudine, an antiviral drug extensively used for combating the global pandemic-HIV/AIDS. The nanocomplex of zidovudine with dextran, stearic acid, and poly (ethylene glycol) was obtained through a double emulsion solvent evaporation method. Further tests

demonstrated the increased cellular internalization of the drug loaded nanoparticles, when compared with the free drug (Joshy et al., 2018).

Chemical modifications permitted the introduction of functional groups that greatly extended the biomedical application of natural dextran (Figure 6). Acetalated dextran (Aca-DEX) **10**, easily prepared from natural dextran, is one of the most commonly used derivatives (Bachelder, Pino, & Ainslie, 2016). A microparticulate-based delivery system prepared by electrospray. The recombinant protective antigen and the adjuvant were encapsulated in acetalated dextran particles, to provide a subunit anthrax vaccine (Gallovic et al., 2016). Depending on the degree and type of acetal modification, the degradation of Aca-DEX can be controlled. Microparticles with tunable degradation rates showed advantages compared to poly(lactic-co-glycolic acid) and iron oxide, two commonly used materials for immunotherapy (Broaders, Cohen, Beaudette, Bachelder, & Fréchet, 2009). Because of its instability at low pH conditions, acetalated dextran was used as acid-responsive biodegradable material. Aca-DEX particles were able to carry either hydrophobic or hydrophilic payloads and released them at mild acidic conditions (pH 5) (Bachelder, Beaudette, Broaders, Dashe, & Fréchet, 2008). Aca-DEX-based microparticles with different hydrolysis rates were used for gene delivery in phagocytic and non-phagocytic cells (J. A. Cohen et al., 2010). Compared with commercially available polyester and poly(L-lactide) (PLA), Aca-DEX nanofiber produced by electrospray gave a faster steady-state doxorubicin (DXR) release. Mice treated with DXR-loaded Aca-DEX resulted in 57% long-term survival (120 days) compared to 20% survival, following treatment with DXR-loaded PLA (Yoo et al., 2018). To increase recognition and subsequent stimulatory effects of toll-like receptor, imiquimod was encapsulated in Aca-DEX microparticles, and rapidly released under acidic lysosomal vesicles. This system is a potent delivery platform for vaccine adjuvants (Bachelder et al., 2010). Aca-DEX nanoparticles, loaded with paclitaxel (PTX), gave sustained release of drug against traumatic spinal cord injury (W. Liu, Quan, et al., 2018). Aca-DEX/camptothecin porous microparticles were prepared via a double emulsion water/oil/water (w/o/w) evaporation method. The tuned particle shape minimized macrophage clearance, favoring lung penetration to deliver the drug to the pulmonary cavity (Meenach et al., 2012). A phenyl acetalated dextran derivative was synthesized and the resulted nanoparticle used as image guided siRNA carrier for cyclooxygenase-2 (COX-2) down regulation. Potential application against auto-immune diseases, gastric inflammation and cancer were suggested (Z. Chen, Krishnamachary, Penet, & Bhujwalla, 2018).

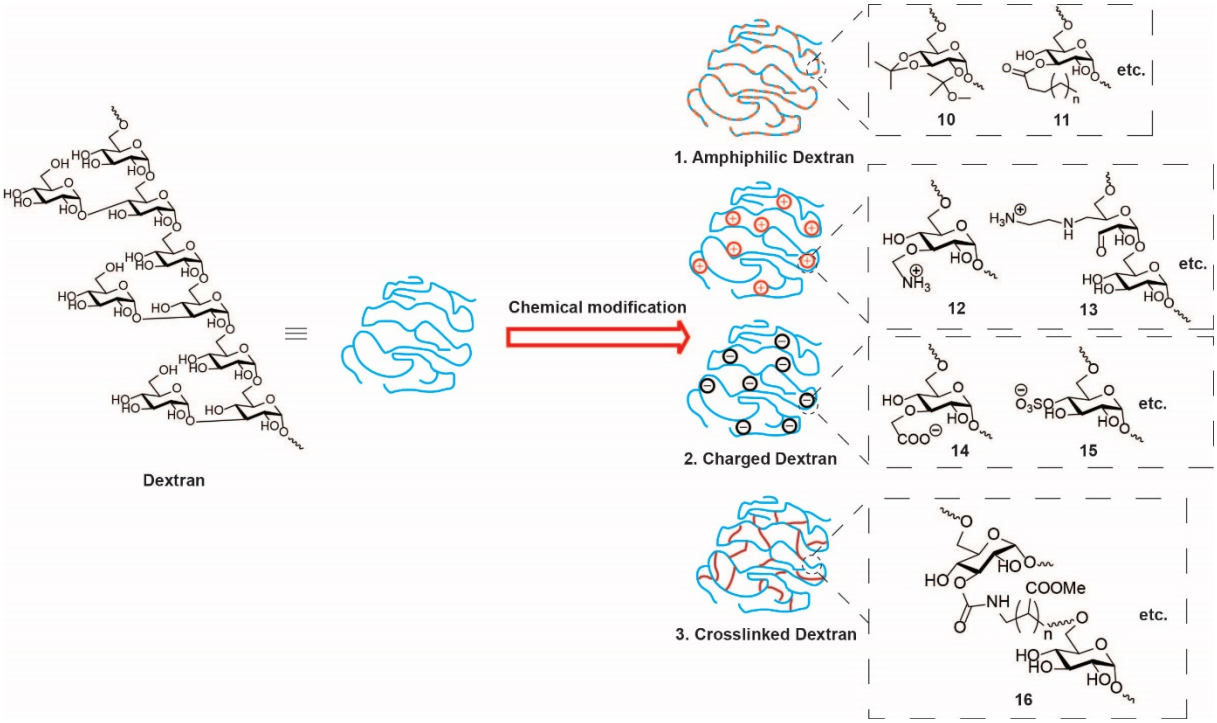

Figure 6: Cartoon depiction of the most common dextran modifications.

Amphiphilic dextran derivatives **11** can be prepared by grafting hydrophobic side chains on the backbone hydroxyl groups (Raemdonck, Demeester, & De Smedt, 2009). Several examples were prepared through esterification with stearic acid (SA) and cholesterol (Chol) and used as carriers to encapsulate rapamycin, a hydrophobic cancer drug. Generally, the particle size increases with increasing particle hydrophilicity (Shaki, Ganji, Kempen, Dolatshahi-Pirouz, & Vasheghani-Farahani, 2018). A dextran based multidrug carrier was developed by adding 3-pentadecylphenol to the dextran side chains. The nano-vesicle can carry, at the same time, the hydrophobic drug camptothecin (CPT) and the hydrophilic drug doxorubicin (DOX), thus improving their synergistic killing of breast and colon cancer cells. This system released its cargo in response to the esterase assisted cleavage in the cell (Pramod, Shah, Chaphekar, Balasubramanian, & Jayakannan, 2014). Monodisperse nanogels were obtained through the self-assembly of amphiphilic poly (D-/L-lactide)-grafted dextran (Nagahama, Mori, Ohya, & Ouchi, 2007). Nanogels composed of dextran and oligolactide (OLA) chains connected via disulfide bonds (Dex-g-SS-OLA) were developed as responsive systems to the reductive cytosol environment, to achieve efficient drug delivery. The addition of galactose (Gal) residues on the nanogel enhanced cellular uptake, by receptor-mediated endocytosis. Further addition of a secondary oligo-amine (tetraethylenepentamine) group promote the escape from the endosomes, acting as a proton sponge (Ohya, Takahashi, & Kuzuya, 2018). Supramolecular hydrogels were prepared though the formation of an inclusion complex between poly(ethylene glycol) grafted dextran and α-cyclodextrins (α-CDs). Interestingly, the complexes showed a unique reversible gel-sol phase transition with hysteresis (Huh et al., 2001). A boronate-linked dextran/cholesterol nanoassembly was prepared for nuclear drug translocation and improved the drug efficacy, as shown with doxorubicin (J.-Y. Zhu et al., 2015). Other cancer targeted drug delivery systems were obtained with translocator protein (TSPO) ligand-dextran conjugates (TSPO-Dex) that formed tightly aggregated particles, with a spherical or rod-like shape (Lopalco et al., 2018). A dextran–platinum (IV) conjugate nanoparticle was used to deliver DOX in a reduction-responsive manner. The collapse of the assembly, due to the reduction of platinum (IV) by glutathione (GSH), triggered the release of DOX. The presence of DOX and Pt(II) was found to be very effective for antitumor therapy (He et al., 2015).

Natural dextran can be oxidized with peroxide or periodate, forming a dialdehyde structure. This modification can be used as handle to form Schiff base linkages **13**. Different amine bearing drugs, such as DOX, can be attached to the dextran nanoparticles and released at low pH, due to the lability of the Schiff linkage (Wasiak et al., 2016). Amphiphilic dextran derivatives, synthesized from oxidized dextran and stearic acid (SA) using different diamines, self-assemble into core–shell micelles. Curcumin was selected as a model drug to show that these dextran carriers have excellent drug loading capacity and drug encapsulation efficiency (Chai et al., 2017).

Hydrophilic modification of dextran with charged functional groups, such as negative carboxylic or sulfuric acids or positive amino groups, can be easily obtained. A dextran sulfate (DS)-based drug delivery system for controlled and sustained release of DOX was developed. This DS-DOX complexes can be further encapsulated into injectable agarose hydrogels and achieve sustained local delivery of low-dose DOX against breast cancer (Niu, Zhang, & Zhong, 2017). With dextran sulfate **15** as the backbone and 5β-cholanic acid, spherical nanoparticles were developed as carrier for methotrexate (MTX) against rheumatoid arthritis (Heo et al., 2017). Interestingly, dextran sulfate was also found to stabilize the positively charged liposome (Cámara, Lurgo, Fanani, & Wilke, 2018). A carboxymethyl dextran **14** hydrogel with porous morphology showed responsiveness to pH and ionic strength of the medium. The diffusion rates of proteins through the hydrogel increased with pH, since repulsion of ionized carboxyl groups enlarge the porous gel structure (Rhongsheng Zhang, Tang, Bowyer, Eisenthal, & Hubble, 2005). A novel, pH-responsive micelle, composed of dextran and poly(oleic acid) side chain was synthesized for oral delivery of nifedipine. The system presents a spherical morphology at critical micelle concentration, and a rod-like assembly beyond that concentration (Karmakar et al., 2018). The modification of dextran with amino groups provides a polycationic biocompatible material especially suitable for gene delivery (Azzam, Eliyahu, Makovitzki, & Domb, 2003), as exemplified by the poly(ethylene imine) (lPEI) grafted onto dextran. An acid-sensitive, biocompatible, microparticulate system based on spermine grafted acetalated-dextran was prepared for siRNA delivery, and achieved efficient gene knock down in HeLa-*luc* cells with minimal toxicity (J. L. Cohen et al., 2011). Additional spermine grafted acetalated dextran-functionalized nanoparticles were developed for dual-drug delivery and targeting of cardiac fibroblasts for cellular reprogramming (M. P. Ferreira et al., 2018). A combination of histidine grafted dextran (Dex-His) and dextran-stearic acid (Dex-SA) was used to construct nano-micelles, to responsively deliver DOX to cancer cells (Jafarzadeh-Holagh, Hashemi-Najafabadi, Shaki, & Vasheghani-Farahani, 2018). A hydrogel based on oxidized dextran and epsilon-poly(L-lysine) showed good adhesive strength against collagen sheets, extending the scope of dextran-based materials to tissue engineering applications (Hyon, Nakajima, Sugai, & Matsumura, 2014). Several systems assembled from two opposite-charged dextran derivatives exist. Hollow nanospheres were prepared from the negatively charged acetic acid grafted on dextran (Dex–CA) 14 and the positively charged ethylamine dextran derivative (Dex–BH) **12**. At pH 5.0, the two components self-assembled into well-defined nanospheres or tubular structures (G. Sun & Chu, 2009). An albumin release study indicates their potential as drug delivery vehicles (G. Sun & Chu, 2011).

Other polymeric backbones crosslinked with dextran **16** also found several applications for drug delivery and tissue engineering. The common strategy is to graft a monomer, such as methacrylate, on the dextran backbone, and perform the polymerization to obtain the crosslinked hydrogel or nanostructures (L. Ferreira, Gil, & Dordick, 2002; Lévesque, Lim, & Shoichet, 2005; G. Sun et al., 2011; T. Wang, Nie, & Yang, 2012; Wei et al., 2017). These strategies can enable further expand the structure and applications of dextran nanomaterials, since the crosslinked material properties are largely affected by the polymer backbones.

Other neutral polysaccharides

Other neutral polysaccharides based on different sugar monomers and glycosidic linkages have been studied. Starch, a storage copolymer based on multiple glucose units, is composed of amylose and amylopectin. Amylose is a poly α-(1-4)-glucoside with a helical three-dimensional structure that can encapsulate hydrophobic molecules in the inner cavity of the helix that in turn stabilizes the helix. Therefore, amylose has been employed for the controlled drug release (Gao et al., 2017; L. Zhang et al., 2016). Amylopectin, glycogen, and pullulan, are branched polyglucosides based on both α-(1-4) and α-(1-6) linkages. They originated from plant, animal and microbial sources, respectively, and have been widely modified for pharmaceutical purposes (Gopinath et al., 2018). Among them, the use of pullulan for drug delivery and tissue engineering has been broadly studied (Singh, Kaur, & Kennedy, 2015; Singh, Kaur, Rana, & Kennedy, 2016). Several modification strategies such as oxidation, esterification, etherification, carboxymethylation, hydroxypropylation, and hydroxyethylation have been used to tune polysaccharide properties (H. Hu, Li, et al., 2016; D. Li, Feng, Chen, Ding, & Chen, 2018; Masina et al., 2017; Tan et al., 2018). The natural polysaccharide dendrimer, glycogen, was studied as a mucoadhesive drug delivery carrier (Perrone, Lopalco, et al., 2017; Perrone, Lopedota, et al., 2017).

Besides glucose, sugar monomers like mannose, galactose, and arabinose are part of other classes of polysaccharides. Of particular relevance, hemicelluloses, composed of xylan and arabinoxylan, inulin, guar gum and locust bean gum have been exploited as a theradiagnostic tool (Braz et al., 2018; George, Shah, & Shrivastav, 2018; W.-Q. Kong et al., 2017; W. Kong et al., 2018; Mandracchia et al., 2017; Petzold-Welcke, Schwikal, Daus, & Heinze, 2014; Rosselgong et al., 2018). Xylan/Polyvinyl alcohol nanofibers prepared by electrospinning possess interesting mechanical and rheological properties. This system was used to improve cardiac cell proliferation for the treatment of myocardial infarction (Soumya, Sajesh, Jayakumar, Nair, & Chennazhi, 2012). Inulin-peptide conjugates self-assembled into micelles, that in response to inulinase, can degrade and release ornidazole, a drug for colon cancer and gastrointestinal disease (Shivhare et al., 2018). The mannose-rich guar gum possess extraordinary mucoadhesive properties and is used in combination with chitosan to form crosslinked hydrogels that serve as transdermal patches for sustained drug-release (Sami et al., 2018).

Charged polysaccharides

Chitosan

Chitin, poly β-(1-4)-*N*-acetylglucosamine, is the second most abundant polysaccharide in nature, mainly constructing exoskeleton of crustaceans, insects, and fungal cell wall. Despite of superior biocompatibility, biodegradability, and physical stability, chitin has been studied rarely for biomedical applications due to water insolubility. To overcome this drawback, chitin is treated with concentrated sodium hydroxide or chitin deacetylase to obtain chitosan, its partially deacetylated derivative (Figure 7). Chitosan is most important derivative of chitin, generally with a degree of acetylation (DA) lower than 50%. The DA, distribution of amine and acetylamine groups, and molecular weight determines solubility and biological activity of chitosan (Aranaz et al., 2014).

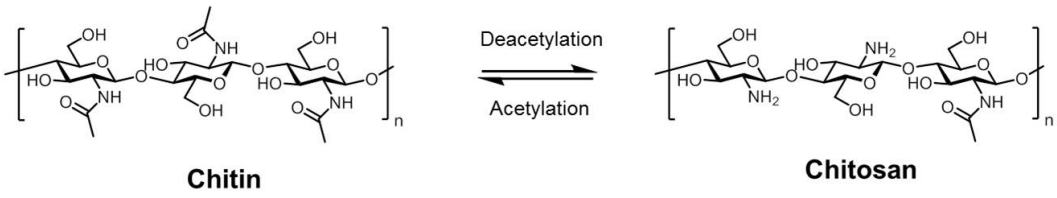

Figure 7: Chitin and its deacetylated analogue chitosan.

Similarly to cellulose, chitin forms strong inter- and intramolecular hydrogen bonds, which hamper its use. In addition, chitin possesses a fibril structure that cannot be solubilized in most organic solvents. Complex solvent mixtures, such as $CaCl_2{\cdot}2H_2O$ saturated methanol, litium chloride/*N,N*-dimethylacetamide (LiCl/DMAc), NaOH/urea, hexafluoroisopropyl alcohol (HFIP), and ionic liquid are employed to disrupt the dense hydrogen bond network of chitin (Ifuku, 2014; Silva, Mano, & Reis, 2017). Ultrafine nanofibers can be obtained by simple solvent evaporation from HFIP solutions or from precipitation induced by addition of water to a LiCl/DMAc solution. These nanofibers are important materials for tissue engineering, as confirmed by *in vitro* cell cytotoxicity and cell proliferation (Zhong et al., 2010). The chitin fibers prepared with HFIP were incorporated in gelatin methacryloyl, forming a ultrastrong and flexible hydrogel applicable in vascular tissue engineering (Hassanzadeh et al., 2016). Chitin solution in $CaCl_2{\cdot}2H_2O$ saturated methanol forms colloidal nanogels, upon addition of excess methanol (Priya, Sabitha, & Jayakumar, 2016). Chitin in NaOH/urea rapidly aggregated into nanofibrous microsphere with high cellular affinity (Duan et al., 2015).

Chitin has been chemically modified to obtain carboxymethyl chitin, glycol chitin, fluorinated chitin, and *N*- and *O*- sulfated chitin. All these modifications aim to improve the water solubility and mechanical properties of natural chitin (Rinaudo, 2006). The carboxymethyl chitin formed nanofiber with poly(vinyl alcohol) via electrospinning (Shalumon et al., 2009). The glycol chitin can easily generate thermosensitive hydrogels in PBS solution (Zhengzheng Li, Cho, Kwon, Janát-Amsbury, & Huh, 2013). Like cellulose, chitin nanofibrils and nanowhiskers have attracted great attention as drug delivery scaffolds (Morganti et al., 2014; Ou, Zheng, Zhao, & Liu, 2018). The most used chitin derivative is chitosan. As the only positively charged natural polysaccharide, chitosan has raised particular interest in biomedical nanotechnology. The positive charge provides antimicrobial, antibacterial, and anticoagulation properties and accelerates wound healing. The amino groups, that can be protonated in acidic conditions, permit to solubilize chitosan. Moreover, pH-responsive systems can be easily created. Mucoadhesive properties and cell permeability are the most important features of this material, enhancing topical, ocular, nasal, and transdermal drug delivery efficiency. The positive charge allows for the adhesion of chitosan-materials to the highly negative mucous environment, through electrostatic interactions. Moreover, the interaction of chitosan with the negatively charged cell wall disrupts the phospholipid alignment and promotes cell penetration (Hamedi, Moradi, Hudson, & Tonelli, 2018; Lin et al., 2018; M Ways, Lau, & Khutoryanskiy, 2018).

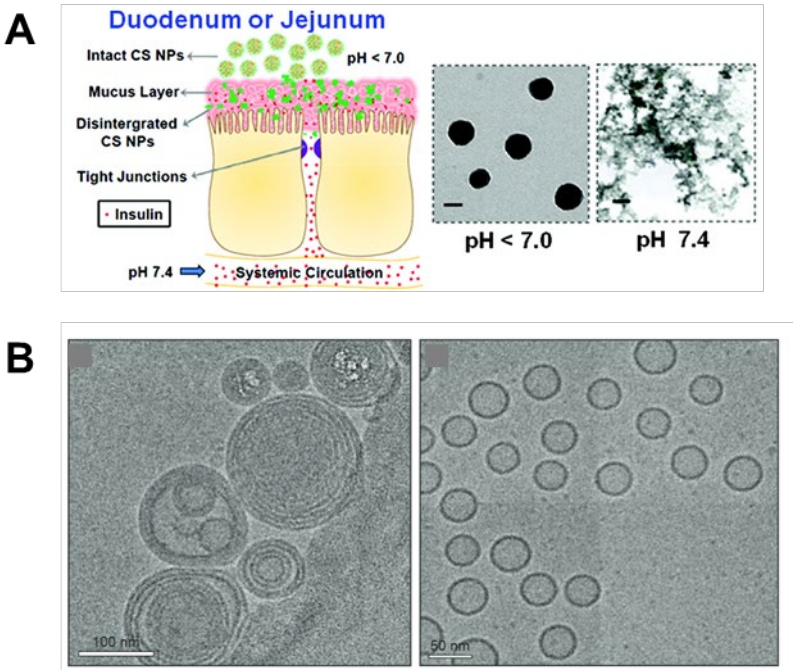

Figure 8: Chitosan nanoparticles for insulin delivery. (A) pH-responsive nanoparticles shield with chitosan for oral delivery (Reprinted with permission from H. Sung et al. (2012). Copyright 2012 American Chemical Society). (B) Multilayered nanoparticles (left) and vesicles (right) encapsulating insulin with coassembly of chitosan and lecithin (Reprinted with permission from L. Liu et al. (2016). Copyright 2016 Dove Medical Press Limited).

The positively charged chitosan was co-assembled with negatively charged compounds, to afford different types of carrier systems (Quiñones, Peniche, & Peniche, 2018). Co-assembly with negatively charged polymers, proteins, and polysaccharides has been tremendously exploited for the formation of drug delivery carriers, especially employed for insulin delivery (L. Liu, Zhou, Xia, & Liu, 2016; Maciel, Yoshida, Pereira, Goycoolea, & Franco, 2017; Sung, Sonaje, Liao, Hsu, & Chuang, 2012; T. Wang, Hou, Su, Zhao, & Shi, 2017; B. Xu et al., 2017)(Figure 8). A layer-by-layer approach, adding repetitively layers of opposite charged compounds one by one, permitted the formation of new materials (L. Li, Wang, et al., 2018).

Countless modifications have been introduced for cell targeting, stimuli responsiveness, and water solubility at neutral pH (C.-H. Chen, Lin, Wu, & Mi, 2018; de Oliveira Pedro, Goycoolea, Pereira, Schmitt, & Neumann, 2018; Lai & Shum, 2015; B. Xu et al., 2017; T. Xu, Xu, Gu, Fang, & Cao, 2018). Chitosan amphiphiles have been prepared by grafting hydrophilic and hydrophobic moieties onto the sugar backbone (J.-Y. Lee, Termsarasab, et al., 2017). Both the amine and/or the hydroxyl groups can be used to functionalize chitosan (Sahariah & Másson, 2017). Three main strategies are used for chitosan functionalization: sulfaltion/sulfonation, amine quaternization, and carboxymethylation. Among them, carboxymethyl chitosan (CMCS), an amphiprotic biopolymer possessing both amine and carboxyl groups, may be the most promising biomedical material with outstanding chemical, physical and biological features. Different types of CMCS such as *N*-CMCS, *O*-CMCS, *N,N*-CMCS, and *N,O*-CMCS are based on different substitution patterns. Each CMCS shows different water solubility and biological activity depending on the degree of carboxymethylation (Upadhyaya, Singh, Agarwal, & Tewari, 2014). CMCS can be assembled into nanoparticles and hydrogels exploiting electrostatic interactions (Al-Rashida, Haider, Kortz, Joshi, & Iqbal, 2018; Song et al., 2018). In particular, self-healing metal crosslinked CMCS hydrogels with high antibacterial activity can be used for tissue engineering and

wound healing (Wahid et al., 2018). Several reviews provide a more detailed description of this topic (Shariatinia, 2018; Upadhyaya, Singh, Agarwal, & Tewari, 2014).

Quaternized chitosan (QCS) in obtained by alkylation of the amines and/or grafting of quaternary ammonium groups to the hydroxyl groups. This functionalization results in permanent positive charges, independent from the pH. *N,N,N*-trimethyl chitosan chloride (TMCS) was the first chitosan derivative bearing *N*-quaternized sites, showing interesting mucoadhesive properties (A. Martins et al., 2014). A TMCS nanoemulsion with dextran sulfate, prepared by hot high-pressure homogenization, successfully delivered a Parkinson's disease drug through the nasal mucosa (Pardeshi & Belgamwar, 2018). TMCS can be additionally transformed to amphiphiles via *N*- and *O*-hydroxyalkylation. *O*-Alkyl TMCS nanomicelles, encapsulating peptide nucleic acid showed hemocompatability and a dramatic increase in cellular uptake (C. Liu, Wang, et al., 2018). Other types of QCS served as pH responsive nanocarriers (de Oliveira Pedro, Hoffmann, et al., 2018; Piras et al., 2018).

Sulfated and/or sulfonated chitosan (SCS) are heparin-like polysaccharides, mainly used for vascularization and bone tissue regeneration (Dimassi, Tabary, Chai, Blanchemain, & Martel, 2018). Implants made of 2-*N*,6-*O*-sulfated chitosan based nanoparticles improved angiogenesis and bone formation with a rich vessel network (Cao, Wang, Hou, Xing, & Liu, 2014). The same compound was used as a coating material for better blood circulation, constructing hierarchical structure with PLGA microsphere (Y. Yu et al., 2015). Glycyrrhetinic acid, a hydrophobic liver-targeting ligand, was attached to SCS and the resulting amphiphile was able to carry doxorubicin and suppress liver cancer (Tian et al., 2012).

Glycosaminoglycans

Glycosaminoglycans (GAGs) are large linear polysaccharides composed of a repeating disaccharide unit (usually an amino sugar and an uronic sugar) (Figure 9). The most common GAGs are hyaluronic acid or hyaluronan **17**, chondroitin sulfate **18**, dermatan sulfate **19**, keratan sulfate **20**, heparin and heparan sulfate **21**. Except for hyaluronic acid, the amino and/or hydroxyl groups of GAGs are modified with *N*-/*O*-sulfation, making the whole structure highly hydrophilic and negatively charged (Esko, Kimata, & Lindahl, 2009). GAGs are widely present on the mammalian cell surface as well as in the extracellular matrix. For this reason, GAGs are popular materials for biomedical studies, as drugs or carriers in drug delivery systems (Fu, Suflita, & Linhardt, 2016; G. Huang & Huang, 2018; Köwitsch, Zhou, & Groth, 2018; Rnjak-Kovacina, Tang, Whitelock, & Lord, 2018; Rodriguez-Torres, Acosta-Torres, & Diaz-Torres, 2018).

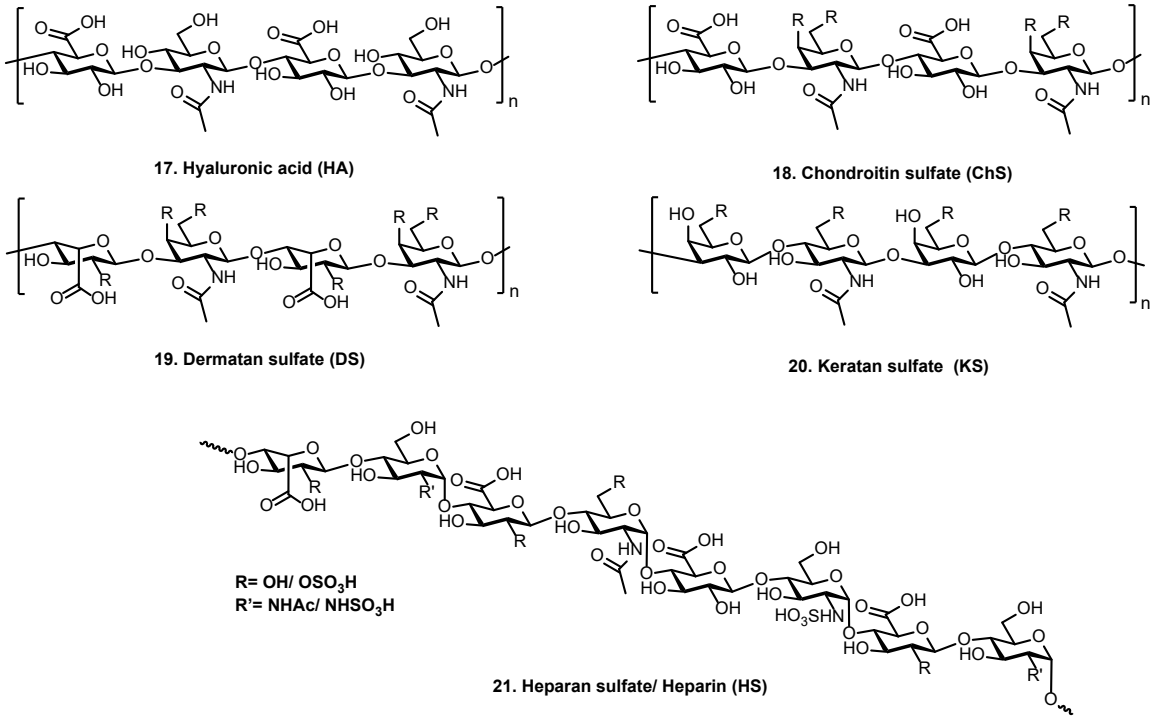

Figure 9: Structures of most common GAGs.

Unlike other polysaccharides, natural GAGs are highly charged, so they can directly serve as carriers for a verity of drugs, without further chemical modifications. Hyaluronic acid (HA)-based doxorubicin (DOX) delivery systems were fabricated through ion-interaction. Spherical nanoparticles (HA-NPs) were prepared from DOX and HA and further assembled into liposomal carriers with lipoid E80 and cholesterol, for CD44+ tumor-targeted delivery (W. Li, Yi, et al., 2016). Chondroitin sulfate (ChS)-nisin nanogel was prepared with different loading and morphology by electrostatic complexation (Mohtashamian, Boddohi, & Hosseinkhani, 2018). Low molecular weight heparin-lappaconitine (LMWH-LA) delivery system was prepared through self-assembly, affording a pH-sensitive drug release (W. Sun et al., 2016). GAGs were co-assembled with positively charged proteins or polysaccharides (e.g chitosan), for clinical applications. Particularly relevant examples are hydrogels with tunable mechanical properties for cell therapy and tissue engineering (Alinejad, Adoungotchodo, Hui, Zehtabi, & Lerouge, 2018), nanoparticles loading doxorubicin for anti-tumor therapy (C.-S. Hu, Tang, Chiang, et al., 2014), nanoparticles for ocular delivery of bromfenac sodium (Abdullah, Ibrahim, & Warsi, 2016), pH responsible hydrogels for theophylline delivery (Lopes, Fajardo, Piai, Rubira, & Muniz, 2013), and protein-loaded nanoparticles (Yeh, Cheng, Hu, Huang, & Young, 2011).

The highly hydrophilic GAGs can be chemically modified with hydrophobic functionalities to create amphiphilic structures, expanding the horizons of GAG nanomaterials (Figure 10). Acetylated chondroitin sulfate, with a high degree of substitution, forms nanogels for DOX delivery (W. Park, Park, & Na, 2010). Hydrophobic modifications on hyaluronic acid greatly affected its self-assembly manners as shown for the octadecylamine-modified HA that formed well-defined hydrophobic domains in its supramolecular structure (Payne, Svechkarev, Kyrychenko, & Mohs, 2018). Oleyl hyaluronan carriers were designed for good skin penetration and large drug deposition in the dermis (Šmejkalová et al., 2017). Amphiphilic nanoparticles, with negatively charged surface, were prepared with a hyaluronic acid–decylamine (HA–DA) conjugates. This system can encapsulate budesonide (BDS) to treat the inflamed intestinal mucosa (Vafaei et al., 2016). Nanomicelles synthesized from hyaluronic acid, ethylenediamine (EDA), hexadecyl chains, polyethylene glycol (PEG), or L-carnitine (CRN) can be used

as imatinib carriers, promoting transcorneal permeation (Bongiovì et al., 2018). Nanocarrier based on α-linolenic acid (αLNA)-grafted hyaluronan (HA) served to deliver hydrophobic drugs (Huerta-Angeles et al., 2016). In the same way, amphiphilic hyaluronan modified with ω-phenylalkanoic ester showed potential applications for resveratrol and retinyl palmitate delivery (Matelová et al., 2016). Systems based on GAG/poly (D, L-lactide-co-glycolide) were also employed for photodynamic therapy (Xiaoling Wang et al., 2018) and doxorubicin delivery (Hui Zhang et al., 2017). Several linkages were used for the amphiphilic functionalization. Spherical hyaluronic acid-doxorubicin particles, connected though hydrazone linkages (HA-hyd-DOX), were designed for acid-triggered release of doxorubicin (Liao et al., 2018). Fluorescein delivery systems, ChS-fluorescein-5-thiosemicarbazide (FTSC) were achieved by carbodiimide chemistry (Varghese, Liu, Sundaram, Hilborn, & Oommen, 2016). HA-riboflavin (Rfv) delivery system was synthesized by click chemistry and used for the delivery of hydrophobic drugs such as dexamethasone, piroxicam and paclitaxel (Manzi et al., 2017). Chondroitin sulfate, directly linked with methotrexate (MTX), afforded a ChS nanogels with increased solubility and improved the delivery efficacy of MTX (J. Wang, Zhao, Chen, Qin, & Zhu, 2017). Dihydroxyflavone-conjugated hyaluronic acid nanogels were prepared and tested for cellular uptake and antitumoral efficiency. The smaller nanogels were taken up by two kinds of tumor cells (HeLa and HepG2) (Choi et al., 2018). Adamantane-grafted hyaluronic acid can work as carrier for methyl-β-cyclodextrin through supramolecular assembly and proved to be a potential antitumor agent (Elamin, Yamashita, Higashi, Motoyama, & Arima, 2018).

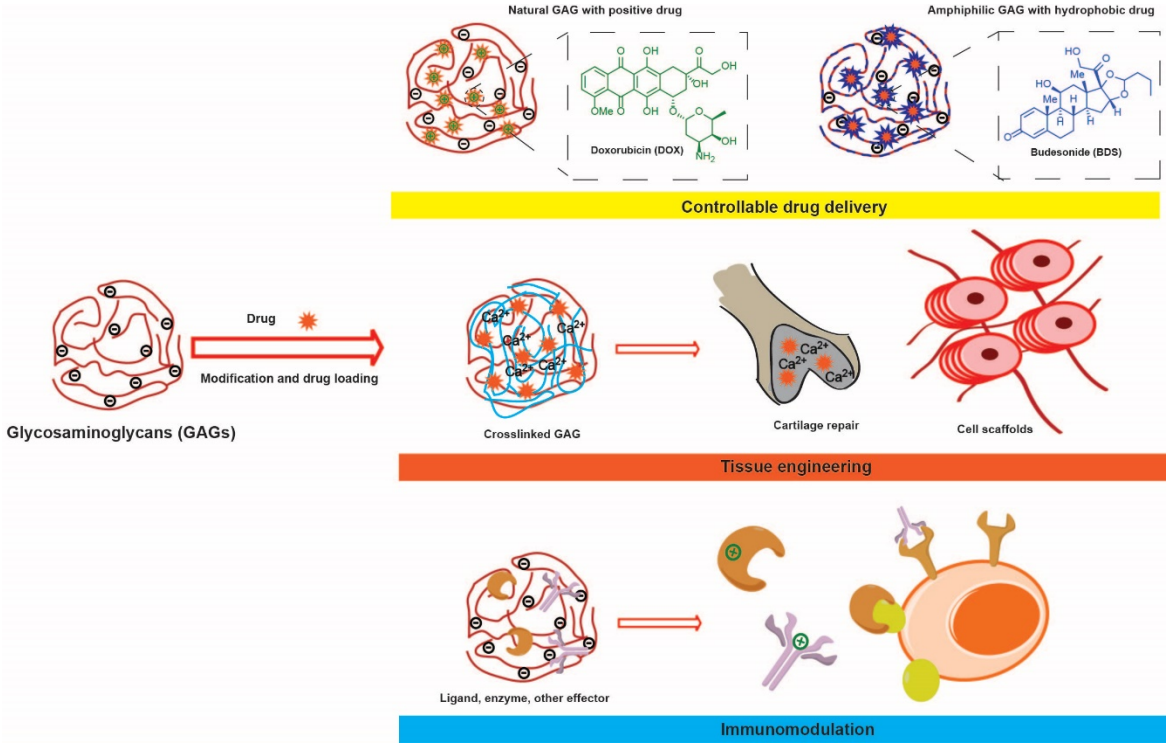

Figure 10: GAGs-based materials and their biomedical applications.

A common functionalization of GAGs is the introduction of disulfide bonds to prepare amphiphilic delivery systems with good biocompatibility and redox-responsive properties (Griesser, Hetényi, & Bernkop-Schnürch, 2018). The conjugation of thiolated hydrophobic molecules to the HA side chain resulted in the formation of nanogels with good immunocompatibility and hemocompatibility (Pedrosa et al., 2016). Fluorescent hyaluronic acid-iodixanol nanogels (HAI-NGs) were used for targeted X-ray computed tomography (CT) imaging and chemotherapy (Y. Zhu et al., 2016). Nanomicelles with hyaluronic acid shell with disulfide-crosslinking were used for the treatment of

multiple myeloma (Gu, Wang, Cheng, Cheng, & Zhong, 2018). Several pH- and GSH-dual-sensitive polymeric conjugate were developed to deliver DOX (Debele, Yu, Yang, Shen, & Lo, 2018; Yin et al., 2018). Redox-sensitive nanoparticles based on heparin-α-tocopherol succinate (Hep-cys-TOS), formed nanoparticles used as carrier for paclitaxel (PTX) (Yang, Cai, Yu, Xi, & Zhai, 2017).

Steroids (or derivatives) with hydrophobic fused ring systems, such as deoxycholic acid (DOCA), cholesterol, and glycyrrhetinic acid (GA), are widely used to fabricate amphiphilic GAG nanostructures. Reduction-sensitive micelles with disulfide linked GAG-DOCA structures were designed for triggered release of DOX (Yang et al., 2017) or docetaxel for the inhibition of metastasis and growth of melanoma (M. Liu, Du, et al., 2018). Spherical micelles with tunable size (124–237 nm) and redox-responsive properties were prepared from amphiphilic chondroitin sulfate-cholesterol conjugates and used as carriers for hydrophobic drugs (C. Yu et al., 2013). DOCA-heparin based micelles, with the pH-sensitive hydrazone bond between DOCA and DOX, enabled both antitumor and antimetastasis activities as well as drug delivery (Mei et al., 2016). Similar systems based on GAG/DOCA were developed in recent years: ChS-DOCA nanoparticles for DOX delivery (J.-Y. Lee, Chung, Cho, & Kim, 2015a), HA-DOCA-histidine micelles for intracellular paclitaxel (PTX) delivery (Yanhua Liu, Zhou, Wang, et al., 2016), phenylboronic acid-decorated ChS-DOCA system for DOX delivery (J. Y. Lee, Chung, Cho, & Kim, 2015b), ChS-DOCA/DOX nanoparticle for the therapy of CD44 receptor-expressing ovarian cancers (J.-Y. Lee et al., 2016), ChS-DOCA conjugates for docetaxel delivery (M. Liu, Du, & Zhai, 2016).

Even though GAGs are highly negatively charged, several examples of functionalization with charged moieties are reported. An iRGD-heparin nanocarrier was synthesized by coupling the heparin backbone with N-end cysteine peptide tumor-homing peptide iRGD. The system can be used as carrier for cis-diamminedichloroplatinum (II) delivery (Ai et al., 2018). A similar heparin-based drug delivery system was prepared by heparin-cis aconitic anhydride ligation. Paclitaxel (PTX) was grafted to the hydroxyl of heparin via an aconitic bond and served as pH sensitive spacer. Positively charged DOX and cationic folic acid (CFA) can be further loaded into the system via electrostatic interaction (Q. Li, Gan, et al., 2016). The amphiphilic chondroitin sulfate-histamine conjugate (ChS-his) can be synthesized and assembled into nanoparticles in aqueous medium and served as pH-sensitive carrier for DOX (C. Yu et al., 2014). Similarly, hybrid nanoparticles based on hyaluronic acid and poly (L-histidine) were used for diagnostic and therapeutic applications (S.-J. Lee & Jeong, 2018).

Chemically and physically crosslinked GAGs possess unique properties in terms of biodegradation and biocompatibility. These features were used to form cell scaffolds, drug delivery systems, and for wound healing (Khunmanee, Jeong, & Park, 2017). In addition, GAG-based hydrogels offer interesting possibilities for bioprinting (Martini et al., 2016). An injectable ionically cross-linked hydrogel was prepared via introduction of alginate to hyaluronate backbones, followed by addition of calcium ions. The gel proved effective in regenerating cartilage in a mouse model (H. Park, Woo, & Lee, 2014). The *N*, *O*-carboxymethyl chitosan/fucoidan conjugate formed a three-dimensional hydrogel based on interconnected macropores, for bone tissue engineering (Lu, Lu, Chen, Lu, & Mi, 2018). Other crosslinking methods for GAGs, such as urea-crosslinked HA systems (Fallacara et al., 2018), poly(ethylene glycol) crosslinked systems (Luo, Kirker, & Prestwich, 2000; Shu, Liu, Palumbo, Luo, & Prestwich, 2004), tyramine (TA) modified HA and ChS systems (Ni et al., 2015) were also developed.

Other charged polysaccharides

In addition to the examples discussed above, several other polysaccharides are commonly used for biomedical materials development. Many of these polysaccharides are charged, highly hydrophilic

glycans (Abedini, Ebrahimi, Roozbehani, Domb, & Hosseinkhani, 2018). In particular, several marine polysaccharides are extracted and used for drug delivery applications (Cardoso, Costa, & Mano, 2016). Carrageenan (CRG) is a highly sulphated linear polygalactan derivative with α-D-galactose and β-1,4/3,6-anhydro-galactose produced by rhodophyceae. Six classes of carrageenans, named Kappa (κ)-, Iota(ι)-, Lambda (λ)-, Mu (μ)-, Nu (ν)- and Theta (θ), exist based on their different structures (Cunha & Grenha, 2016). CRG hydrogels are popular choices for drug delivery, tissue engineering and wound healing (Yegappan, Selvaprithiviraj, Amirthalingam, & Jayakumar, 2018). The preparation of microspherical κ-carrageenan gel particles, using emulsion technology, affects the final aerogel properties (Alnaief, Obaidat, & Mashaqbeh, 2018; Obaidat, Alnaief, & Mashaqbeh, 2018). κCRG-based drug carriers were developed (Obaidat et al., 2018; Sathuvan et al., 2017). Carboxymethylated ι-carrageenan was chosen to deliver amphotericin B against the intracellular *Candida glabrata* infections (Aparna et al., 2018). Moreover, the combination of CRG with other polysaccharides was exploited for biomedical applications. Relevant examples are the cross-linked starch-κ-carrageenan hydrogel for extended release of zaltoprofen (Sonawane & Patil, 2018), the glucan/carrageenan hydrogels for wound healing (Nair, Raman, & Doble, 2016), and the κ-carrageenan/chitosan nanosystems for drug delivery (Amarnath Praphakar et al., 2017; Karimi, Mahdavinia, & Massoumi, 2018; Mahdavinia, Mosallanezhad, Soleymani, & Sabzi, 2017; Rochín-Wong et al., 2018).

Alginate (alginic acid) is a linear polysaccharide consisting of D-mannuronic acid and L-guluronic acid units, isolated from phaeophyceae (Tønnesen & Karlsen, 2002), that was used the formation of several delivery systems. Moreover, injectable hydrogels of phosphorylated alginic acid-calcium complexes were developed for soft tissue engineering (H.-S. Kim, Song, Lee, & Shin, 2015). Cross-linked alginate provides additional options to construct nanocarriers with different functions. The hydrophobically modified alginic acid, crosslinked by 1,10-decanediol, was proven to be a good carrier for ibuprofen (M. Wu et al., 2013). Similarly, albumin-crosslinked alginate hydrogels were prepared to deliver positively charged drugs (Tada, Tanabe, Tachibana, & Yamauchi, 2007).

Ulvan, a cell-wall polysaccharide from green seaweeds, is mainly composed of a disaccharide repeating unit of uronic acid (D-glucuronic or L-ioduronic) and L-rhamnose-3-sulfate (Morelli & Chiellini, 2010). Upon functionalization with methacryloyl moieties and photopolymerization, ulvan forms hydrogels used as matrix for cell encapsulation (Morelli & Chiellini, 2010). A similar strategy was used to produce thermosensitive hydrogels (Morelli, Betti, Puppi, & Chiellini, 2016) and scaffolds for bone tissue engineering (Dash et al., 2014). Lysozyme/ulvan complexes can be prepared through ionic interactions at physiological pH, showing good antibacterial activity (Tziveleka et al., 2018). Ulvan/chitosan systems were used as polymeric components of bone cements (Barros et al., 2013) and for the cultivation of osteoblasts (Toskas et al., 2012).

Plants also contain numerous useful polysaccharides for pharmaceutical applications. Pectin is one of the most structural complicated polysaccharides in nature; it is rich in galacturonic acid and contains different rare sugar units (Caffall & Mohnen, 2009). Pectin is generally used in combination with other polysaccharides to produce materials for drug delivery. Bacterial cellulose–high methylated pectin films were developed to encapsulate and release biomacromolecules such as human serum albumin (Cacicedo et al., 2018). Alginate–pectin polymeric rafts showed pH-responsive property and showed potential for the treatment of gastro-esophageal reflux disorders (Hanif & Abbas, 2018). Chitosan, due to its negative charge, was also widely used to prepare different nanostructures, in combination with pectin. Relevant examples are micelles based on self-assembling chitosan cross-linked pectin–doxorubicin conjugates (Z.-P. Li, Jiang, et al., 2018), pectin-chitosan membrane scaffolds for the

controlled stem cell adhesion and proliferation (J. G. Martins et al., 2018), and electrospun pectin-oligochitosan nanofibers for tissue engineering (McCune et al., 2018).

Gum arabic from the *Acacia senegal* and *Acacia seyal* trees is a branched heteropolysaccharide with a 1, 3-linked β-D-galactopyranose backbone and L-arabinose, L-rhamnose, or D-glucuronic acid branching. It shows important biomedical properties, including antimicrobial, anti-inflammatory, and anticoagulant activity (Patel & Goyal, 2015). Alginate-gum arabic hydrogels, crosslinked with Ca^{2+}, showed potential applications for wound healing (M. Li, Li, et al., 2017). Additionally, pH-sensitive delivery systems were obtained from the cross-linking of carboxymethyl chitosan–gum Arabic (G.-Q. Huang, Cheng, Xiao, Wang, & Han, 2016).

Gellan gum is a bacterial extracellular polysaccharide secreted by *Pseudomonas elodea*, which contain a tetrasaccharide repeating unit with α-L-rhamnose, β-D-glucuronic acid, and two β-D-glucoses (Osmałek, Froelich, & Tasarek, 2014). It was used in ocular delivery systems (Paolicelli et al., 2018; J. Sun & Zhou, 2018), cutaneous delivery systems (Musazzi et al., 2018), and for antibiotic delivery during wound healing (Shukla & Shukla, 2018). Additionally, oxygen-producing biomaterials were developed based on gellan gum (Newland et al., 2017). Chitosan-gellan gum systems (S. Kumar, Kaur, Bernela, Rani, & Thakur, 2016), and pectin-gellan gum systems (Bera, Kumar, & Maiti, 2018; Fernandes, Fortes, da Cruz Fonseca, Breitkreutz, & Ferraz, 2018; Prezotti et al., 2018) are popular choices for smart drug delivery systems. Xanthan gum is a microbial polysaccharide produced by *Xanthomonas* bacteria; it is negatively charged and widely used for tissue engineering (A. Kumar, Rao, & Han, 2018) and drug delivery (Salamanca, Yarce, Moreno, Prieto, & Recalde, 2018). Xanthan gum-chitosan nanofibers (Shekarforoush, Ajalloueian, Zeng, Mendes, & Chronakis, 2018), gellan-xanthan systems (Ramburrun, Kumar, Choonara, du Toit, & Pillay, 2017; Sehgal, Roohani-Esfahani, Zreiqat, & Banerjee, 2017), and -xanthan gum hydrogels perform great in biomedical applications (Ruquan Zhang et al., 2018).

Conclusion

Due to their natural abundance and tendency to form supramolecular networks, carbohydrates are important substrates for biomedical applications. Several materials, based on simple monosaccharides or complex polymers have been synthesized. Tunable properties can be achieved through chemical modifications as well as assembly conditions. A plethora of morphologies, from spherical particles to nanogels, can be obtained. Due to their biocompatibility, those materials found several applications in drug delivery and tissue engineering. Recently, the attention has been directed to the formation of responsive drug delivery systems. Very stable assemblies have been developed, that are able to target particular cells and decompose in response to external stimuli, such as pH or salt concentration, to release the cargo. Similarly, the reversible association of carbohydrate-based nanomaterials is particularly useful for implants and tissue engineering.

The variety of natural carbohydrates, from monosaccharides, to cyclic systems, as well as long charged or neutral polymers has given rise to a range of materials with tunable properties. Chemical modifications have further expanded the range of applications. Reproducibility is the main challenge in the carbohydrate materials field. Polysaccharides are generally extracted from natural sources, often in low purity and high polydispersity. Control on the degree of substitution and polymerization are serious challenges that have to be addressed, in order to achieve more reproducible results. Moreover, a deeper understanding of how to regioselectively modified natural polysaccharides is needed. Purely synthetic, well-defined systems are limited to mono- and disaccharides. With the development of synthetic techniques that allow for quick access to longer oligosaccharides, new

glycomaterials can be envisioned. Well-defined derivatives will help to establish the relationship between polysaccharide structure and its assembling behavior, opening the way to novel and reproducible biomedical applications.

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