Polysaccharides-based nanohybrids: Promising candidates for biomedical materials

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Natural polysaccharides are the polymers composed of monosaccharides through glycosidic bonds. Diverse polysaccharides could be readily obtained from algae (such as alginate), plants (such as pectin), microbes (such as dextran) and animals (such as chitosan (CS)). Carrying abundant functional groups including free carboxyl and hydroxyl groups, natural polysaccharides possess outstanding merits including biocompatibility, low toxicity, stability, low cost, and availability for versatile chemical modification [1,2]. Therefore, polysaccharides have been considered as promising building blocks for biomedical applications including drug delivery, gene delivery, imaging and targeted therapy [3]. Different types of polysaccharides with multiple structures result in favorable properties. For instance, positively charged CS could interact with negatively charged molecules and mucosal surfaces. Moreover, CS demonstrates antibacterial properties since it could associate with anions on the bacterial cell wall to suppress biosynthesis and disrupt the mass transport across the cell wall to accelerate the death of bacteria [4,5]. Highly water-soluble dextran is resistant to protein adsorption and could avoid nonspecific cell binding [1]. Negatively charged hyaluronic acid (HA) has been widely used as a targeting agent, due to the interaction with CD44 receptor which is overexpressed in tumors. HA was also found to play an important role in cell growth, healing processes, and inflammation. Neutral pullulan was reported to possess inherent liver-targeting property so that it could be utilized to target hepatoma cells with asialoglycoprotein receptor (ASGPR) overexpression [6]. In addition to polysaccharides and their derivatives, polysaccharides-based nanoparticles (NPs) have also drawn much attention which could be prepared

via cross-linking, polyelectrolyte complexation, and self-assembly strategies for biomedical applications [2,3]. Although the prospects are promising, the great potential of polysaccharides in the fabrication of multifunctional systems still remains to be investigated. Therefore, it is necessary to exploit new types of polysaccharides-based biomaterials taking advantage of their facile chemical functionalization.

Inorganic NPs such as gold, silica, quantum dots (QDs), graphene and iron oxide NPs hold favorable optical, magnetic, and electrical properties, which have been utilized in biomedical areas to introduce versatile functions [7]. In terms of optical properties, the localized surface plasmon resonance (LSPR) effect of Au NPs is well-known. When the LSPR absorption locates in the near infrared (NIR) region, heat will be induced by light irradiation to realize photothermal therapy (PTT), photothermal imaging, and photoacoustic (PA) imaging [8]. Fluorescent QDs with size-tunable and narrow-band emission are ideal candidates for fluorescence (FL) imaging *in vitro* and *in vivo*. Graphene nanosheet possessing extended aromatic system could deliver small molecule drugs/nucleotides/peptides *via* π - π and hydrophobic interactions [9]. Moreover, graphene nanosheet could work as photosensitizer with high NIR light absorbance for potential PTT [9]. Magnetic iron oxide NPs could integrate magnetic targeting, magnetic resonance (MR) imaging, and magnetic hyperthermia therapy in the presence of alternative magnetic field [10–12]. More interestingly, certain types of NPs including iron oxide NPs and Au clusters exhibit intrinsic enzyme-like activity [13,14]. Moreover, compared with organic components, it is easier to control the size and shape of inorganic NPs

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while the surface modification with organic ligands is essential to attain stability and biocompatibility [15]. In this regard, it would be desirable to construct polysaccharides-based nanohybrids composed of flexible polysaccharides and versatile inorganic NPs (Fig. 1). It could be imaged that the combination of complementary properties of both components will realize multi-functions for satisfying applications. Furthermore, synergistic effect might be achieved due to their integration at the nanoscale. Taking advantage of the enhanced permeation and retention (EPR) effect, polysaccharides-based nanohybrids could preferentially accumulate around the tumor regions. All these merits render polysaccharides-based nanohybrids promising candidates in biomaterial field.

Typically, three methods are employed to construct polysaccharides-based nanohybrids, namely surface functionalization, one-pot synthesis, and wrapping [8]. Surface functionalization of inorganic NPs with polysaccharides offers a powerful strategy to achieve nanohybrids. HA functionalized silica NPs were prepared through the conjugation of HA on the surface of silica by cleavable disulfide bonds. Dual-stimuli responsiveness to glutathione and hyaluronidases could be realized in the nanohybrids for controlled drug release and targeted delivery [16]. One-pot synthesis is a convenient and straightforward strategy to produce polysaccharides-based nanohybrids where the polysaccharides usually play the role of surface capping agents or reactants. For example, Jang *et al.* [17] designed dextran-Au nanohybrids for effective delivery of doxorubicin (DOX), where dextran worked as both reducing agent and capping agent. Wrapping is also widely used for the fabrication of polysaccharides-based nanohybrids. A series of multi-

functional nanohybrids composed of CS and versatile inorganic NPs were prepared through facile nonsolvent-aided counterion complexation method, including Au nanorods [18], carbon dots [19] and magnetic NPs [20]. Taking advantage of electrostatic interaction between CS and ethylene diamine tetraacetic acid (EDTA) and non-solvent ethanol, CS nanospheres could be obtained. In a similar way, CS-Au nanohybrids could be fabricated in the presence of gold nanorods (Fig. 2) [18].

Polysaccharides-based nanohybrids usually possess physiological stability, biocompatibility and compromised toxicity owing to the introduction of polysaccharides [21]. Meanwhile, the intriguing characteristics of inorganic NPs bring unique optical, magnetic, and electrical properties to the nanohybrids. Benefiting from the crosslinking of abundant functional groups (such as hydroxyl and amine groups), the matrix of polysaccharides could also realize stimuli-responsiveness, which could facilitate the effective treatment in the specific tumor region [22]. For example, pH-responsive self-destruction of polysaccharides-Au nanohybrids was realized through the cleavage of Schiff base bonds in the matrix [6]. In addition, the porous network of polysaccharides formed by cross-linking or host-guest interaction could not only wrap inorganic NPs, but also load guest molecules such as drugs and photosensitizers [18,19,23]. Moreover, the payload of charged drugs could also be facilitated by sulfonated CS-Au nanohybrids *via* electrostatic interaction [24]. The multiple groups of polysaccharides could also be used to conjugate therapeutics. In addition, the inherent targeting property of certain polysaccharides endows the nanohybrids with the ability to accumulate in specific locations [6,25]. On the other hand, inorganic parts of the nanohybrids usually incorporate the func-

Figure 1 Polysaccharides-based nanohybrids composed of flexible polysaccharides and versatile inorganic NPs.

Figure 2 Schematic showing the formation of CS-Au nanohybrids. Reproduced with permission from Ref. [18]. Copyright 2013, Elsevier.

tions of fluorescence, MR or PA imaging, magnetic targeting and PTT. More interestingly, the combination of the polysaccharides and inorganic NPs could produce some synergistic properties. For instance, CS-ZnFe₂O₄

nanohybrids presented improved contrast in T_2 weighted MR imaging and sensitivity in the tumor sites compared with separate NPs due to the tightly packed magnetic NPs in CS matrix [20]. The release of drug in CS-carbon dot nanohybrids could be triggered by NIR light due to the photothermal property of carbon dots (Fig. 3) [19].

The morphology of nanohybrids including size and shape is considered to affect their properties and functions, such as cellular uptake, biodistribution, delivery efficiency and imaging capability [8,26]. For example, nanohybrids with rough surfaces were found to possess higher gene transfection efficiency and antitumor effectiveness compared with the smooth counterparts [27]. However, most polysaccharides-based nanohybrids are spherical and the morphology effect of polysaccharides-based nanohybrids is rarely investigated up to now. It will be interesting to reveal the relationship between the properties and morphology of polysaccharides-based nanohybrids.

Figure 3 (a) Schematic of DOX-loaded CS-carbon dot nanohybrids for therapeutic application. (b) Schematic of chemotherapy alone or combined photothermal-chemo therapy on cancer cells using nanohybrids as drug carriers. (c, d) *In vitro* cytotoxicity of 4T1 cells and therapeutic efficacies of nanohybrids for different treatments. Reproduced with permission from Ref. [19]. Copyright 2017, American Chemical Society.

Polysaccharide-based nanohybrids have been explored for versatile biomedical applications including diverse imaging and therapies. Generally speaking, multi-functions will be achieved in the same nanohybrid. Wang *et al.* [19] reported a type of CS-carbon dot nanohybrids by integrating pH-sensitive chitosan and fluorescent carbon dots for simultaneous NIR imaging and NIR/pH dual-responsive drug release to improve therapeutic efficacy. Synergistic PTT/chemotherapy was attained by CS-Au nanohybrids due to enhanced cytotoxicity of the loaded cisplatin at elevated temperature arising from photothermal property of Au nanorods [28]. Redox-responsive HA-graphene oxide nanohybrids were successfully developed through the rational design of disulfide linkages.

Graphene oxides introduced enhanced loading of doxorubicin and photothermal effect while HA guaranteed active tumor targeting. In addition, the digestion of HA in the presence of hyaluronidase accelerated redox-triggered drug release from nanohybrids for efficient tumor treatment [25]. It is worth mentioning that polysaccharides-based nanohybrids have also been employed for anti-infective therapy. Dextran-iron oxide nanohybrids were found to exhibit enzyme-like catalytic activity at acidic pH, which could work as nanozymes. Furthermore, the nanohybrids possess surprising capability to target biofilms with high specificity originating from the selective binding of dextran coating to bacterial cells. The dextran-iron oxide nanohybrids were verified to catalyze hydro-

Figure 4 Antibiofilm properties of topical dextran-iron oxide nanohybrids + H_2O_2 treatments (gray: bacteria, green: nanohybrids, magenta: exopolysaccharides). Reproduced with permission from Ref. [13]. Copyright 2019, American Chemical Society.

gen peroxide (H_2O_2) to produce hydroxyl radicals for pH-activated biofilm disruption, which is promising for the treatment of oral biofilm-associated infection (Fig. 4) [13].

As promising biomaterials, polysaccharides-based nanohybrids also face great challenges and obstacles for potential clinical applications. From the perspective of preparation, the controllability of nanohybrids should be improved since most design and synthetic procedures are relatively delicate and complicated considering the reproducibility and facile scale-up for production. Another challenge is the tolerance of nanohybrids in complex physiological environments. Although the nanohybrids are considered biocompatible and stable owing to the virtues of polysaccharides, their behaviors in the body remain to be investigated. How to ensure that the targeting of polysaccharides maximizes the accumulation of material in the lesion? Will the responsiveness of nanohybrids accurately distinguish lesions? Could the nanohybrids be cleared from the body without adverse effect? Whether the drug loaded by nanohybrids could be controllably released in the lesion? All these questions require a better understanding of the fundamental mechanism of nanohybrids. In addition, the exploration of the functionalization of polysaccharides-based nanohybrids is still limited. The abundant functional groups could be taken full use for the rational design of the nanohybrids. The morphology control of the nanohybrids is also to be studied taking advantage of the structure and property of inorganic NPs. More importantly, the synergistic properties from the polysaccharides and inorganic NPs are expected to reveal the appealing feature of the nanohybrids. Using these design concepts, the development of new types of nanohybrids will also help understand the interactions between the nanohybrids and cells or tissues. Currently, nanohybrids have been applied in a variety of biomedical areas including anti-infective therapy. The progress in concept of design, preparation, and fundamental mechanism will in turn widen the application of the nanohybrids in imaging and therapy. Overall, we believe polysaccharides-based nanohybrids have demonstrated great potential as promising biomaterials and may open a new avenue on the construction of advanced biomaterials for practical applications.

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多糖基复合纳米材料: 有希望的候选生物医用材料

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摘要 由多糖和多功能无机纳米颗粒组成的多糖基复合纳米材料在生物医学领域具有潜在的应用价值, 是一种有希望的候选材料. 本文介绍了多糖基复合纳米材料的优良性能及其在成像和治疗中的应用. 除了多糖和无机纳米颗粒这两部分的功能简单结合以外, 复合纳米材料还具有协同性能和功能. 最后, 我们讨论了多糖基复合纳米材料在潜在的临床应用中的挑战和前景.