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Polysaccharide-based nanomedicines for cancer immunotherapy: A review

Yujun Zeng [a,1], Yufan Xiang [a,1], Ruilong Sheng [c], Helena Tomás [c], João Rodrigues [c], Zhongwei Gu [a,b], Hu Zhang [d], Qiyong Gong [a,b], Kui Luo [a,b,*]

[a] Huaxi MR Research Center (HMRRC), Department of Radiology, Department of Neurosurgery, Functional and Molecular Imaging Key Laboratory of Sichuan Province, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, 610041, China
[b] Research Unit of Psychoradiology, Chinese Academy of Medical Sciences, Chengdu, 610041, China
[c] CQM-Centro de Quimica da Madeira, MMRG, Universidade da Madeira, Campus da Penteada, 9000-390, Funchal, Madeira, Portugal
[d] Amgen Bioprocessing Centre, Keck Graduate Institute, Claremont, CA, 91711, USA

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ABSTRACT

Cancer immunotherapy is an effective antitumor approach through activating immune systems to eradicate tumors by immunotherapeutics. However, direct administration of "naked" immunotherapeutic agents (such as nucleic acids, cytokines, adjuvants or antigens without delivery vehicles) often results in: (1) an unsatisfactory efficacy due to suboptimal pharmacokinetics; (2) strong toxic and side effects due to low targeting (or off-target) efficiency. To overcome these shortcomings, a series of polysaccharide-based nanoparticles have been developed to carry immunotherapeutics to enhance antitumor immune responses with reduced toxicity and side effects. Polysaccharides are a family of natural polymers that hold unique physicochemical and biological properties, as they could interact with immune system to stimulate an enhanced immune response. Their structures offer versatility in synthesizing multifunctional nanocomposites, which could be chemically modified to achieve high stability and bioavailability for delivering therapeutics into tumor tissues. This review aims to highlight recent advances in polysaccharide-based nanomedicines for cancer immunotherapy and propose new perspectives on the use of polysaccharide-based immunotherapeutics.

1. Introduction

Cancer is one of the major diseases with high prevalence, severe symptoms and clinical manifestations, unfavorable treatment responses and poor prognosis, thus early diagnosis and effective treatment of cancer are a hotspot that has attracted great attention. Currently, clinically practical and effective treatment methods for cancer are focused on surgery, chemotherapy, radiotherapy and immunotherapy, which are known as the four pillars of cancer treatment [1]. Among them, immunotherapy, using human immune systems to treat cancer, blocks certain immune inhibitory checkpoints or pathways [2,3], promote T cells killing ability towards tumor cells (i.e. CAR-T therapy) [4,5] and increase innate immune processes by tumor associated macrophages (TAMs) and natural killer (NK) cells [6,7] to accomplish targeting immune suppression or elimination of tumor cells. Some of these immunotherapy strategies have been adopted in clinical practices and demonstrated to be efficacious for cancer diseases. The emergence of new therapeutic targets [1,8,9] or new strategies [10–12] to improve the efficacy and reduce the side effect of immunotherapy are becoming attractive in cancer treatment. However, since tumor immunity is a complex process that is not fully understood yet, this emerging immunotherapy is facing great challenges such as a low targeting efficacy, which would reduce the therapeutic effect of administrated drugs, and intrinsic toxicities of immunotherapeutic drugs, which could cause severe inflammatory and autoimmune diseases [13–15]. In this context, many attempts have been made to improve the efficiency/efficacy of cancer immunotherapy while minimizing its side effects [16,17]. One of the most promising approaches is to apply nanomaterials as carriers for immunotherapeutic agents.

With the rapid growth of nanobiotechnology, nanomaterials have become more and more clinically applicable for medical treatment [18,19]. These nanomaterials with a size of 10–500 nm are able to increase the therapeutic efficacy and reduce the toxicity of therapeutic drugs by encapsulating or conjugating them to form stabilized nanomedicines

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* Corresponding author. West China Hospital, Sichuan University, Chengdu, 610041, China.
E-mail address: luokui@scu.edu.cn (K. Luo).
[1] These authors contributed equally.

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[20,21]. These nanomedicines selectively penetrate into tumor tissues and achieve controlled, efficient and sustained drug release. All these advantages of nanomaterials earn them a space in the arena of cancer diseases treatment [22,23]. Studies [24–26] have also demonstrated that nanomaterials could encapsulate or conjugate immunotherapeutic antigens, adjuvants, genes or antibodies to act as cancer nanovaccines that could improve the efficacy of cancer immunotherapy (Fig. 1) while reducing toxicity and side effects of these managed drugs. Among these applied nanomaterials are polysaccharide-based nanosystems.

Because polysaccharides are biocompatible and biodegradable, thus relatively safe to be applied in medical practices, polysaccharide-based nanosystems have attracted significant attention as delivery platforms for the treatment of various diseases [27,28]. The effectiveness of polysaccharide-based nanomedicines in improving the antitumor therapeutic efficacy has been demonstrated [29,30]. Polysaccharide-based nanoparticles could bypass adenosine triphosphate (ATP) binding cassette transporters and are internalized into targeting cells such as microfold cells or CD44 overexpressing tumor cells [31,32]. Since systemic administration of many antitumor drugs such as cisplatin, paclitaxel, and doxorubicin would result in severe side effects like hepatotoxicity, nephrotoxicity, neurotoxicity or hypersensitivity reactions [33,34], this targeting polysaccharide-based nanosystem could deliver these antitumor drugs only into selective cells to increase their therapeutic efficacy, and reduce the toxicity and the incidence of side effects. In addition, it has also been reported that some polysaccharides could stimulate intrinsic antitumor immune systems themselves [35–37], thus triggering more studies on polysaccharide-based nanomedicines for cancer immunotherapy.

Regarding to this, functional nanomaterials based on chitosan, hyaluronic acid (HA), dextran, alginate and other polysaccharides have been explored as potential drug delivery platforms for immunotherapeutic agents and a few polysaccharides have been acted as immune adjuvants themselves for cancer treatment (Tables 1–3). A few review articles about polysaccharide-based nanomaterials and their biological applications or polysaccharide-derived nanomedicines for cancer therapy have been published in the past years. Two reviews in 2015 [38,39] and another two in 2018 [40,41] thoroughly discussed the immunological responses of polysaccharides and their potential for immunotherapy. Another four reviews in the past 6 years on the other hand provided an overview of how nanomaterials can be beneficial for cancer immunotherapy [24,42–44]. However, none of these reviews have specifically discussed the role of polysaccharide-based nanomedicines for cancer immunotherapy. Thus this review aims to provide an overview of various natural polysaccharide-based immunotherapeutic delivery nanosystems and their cancer immunotherapy applications. The types of polysaccharides, their delivery nanosystems for immunotherapeutic agents, mechanisms of immune-activation/suppression at the molecular level, as well as their immunotherapeutic effects are described and discussed.

2. Cancer immunotherapy and potential role of polysaccharides and their derivatives

2.1. Current status of cancer immunotherapy

In response to tumor genesis and growth, living bodies can generate immune responses to eliminate these tumor cells, this immune stimulatory effect is usually insufficient to eradicate tumor cells completely, and tumor tissues continue to grow and metastasize [67–69]. External immunostimulators and immunomodulators are often required to evoke a strong immune reaction that could effectively suppress or eliminate tumor cells [70–72]. . To achieve cancer immunotherapy, currently there are three major immunity stimulating and enhancing methods for cancer, including immune cell therapy, antibody therapy and cytokine therapy. Immune cell therapy applies genetically modified immune cells to patients to provoke antitumor responses. Chimeric antigen receptor T (CAR-T) cell therapy has been successfully commercialized for liquid cancer, and US Food and Drug Administration (FDA) approved CAR-T therapeutics include Breyanzi (Juno Therapeutics), Kymriah™ (Novartis) and Yescarta™ (Kite Pharma). By transducing the CAR gene into T cells through viral vectors, CAR-T cells could specifically recognize tumor cells and initiate a strong immune attack towards them [73]. Provenge (Sipuleucel-T) developed by Dendreon Pharmaceuticals is another approved cellular product for immune cell therapy, and dendritic cells (DCs) instead of T cells are used in this product [74]. Monoclonal antibodies are used as immunotherapeutics for antibody therapy. After formation of B-cell and myeloma-cell complexes with unique tumor antigens on myeloma cells, the generated monoclonal antibodies could specifically target tumor cells, resulting in strong tumor immune stimulation and modulation. This is achieved through antibody-dependent cell-mediated cytotoxicity (ADCC) directly towards tumor cells, or by stimulating the complement system to activate the membrane attack complex. FDA approved therapeutics with this mechanism include Rituximab [75], Alemtuzumab [76], Ofatumumab

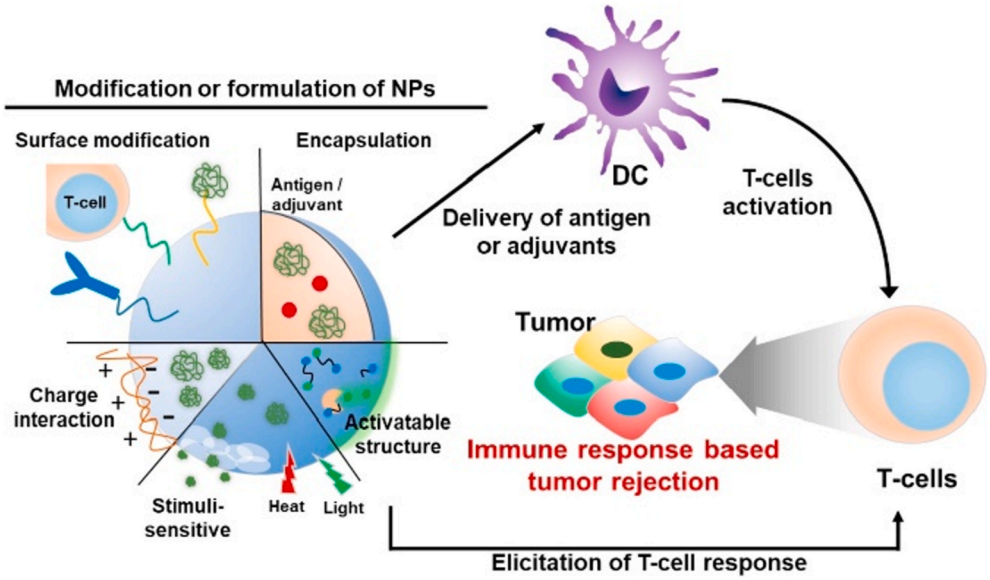
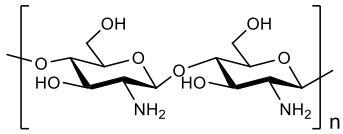
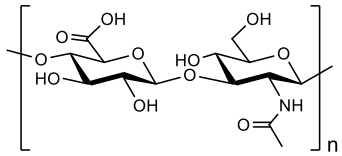
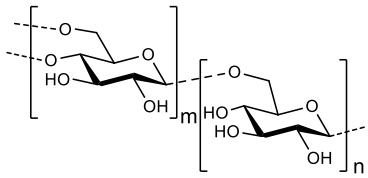
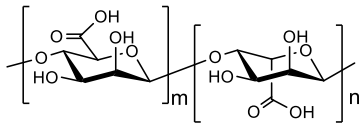


Fig. 1. Schematic diagram for the use of nanoparticles to promote cancer immunotherapy. Several modifications and formulation strategies of nanoparticles enable them to deliver antigens or adjuvants with a higher delivery efficacy and a lower off-target effect. These therapeutic agent-loaded nanoparticles could maturate antigen presenting cells like dendritic cells (DCs) so as to activate tumor killing T cells. Some nanocomposites could also directly act on T cells to promote their tumor killing effect. Reproduced with permission from Ref. [45]. Copyright 2018 Elsevier.

Table 1
Polysaccharides in the nano-based cancer immunotherapy and their structure and advantages.

Polysaccharide Type	Structure	Advantages
Chitosan		high biodegradability; excellent biocompatibility; great bioactivity; non-toxicity; pH-responsiveness; flexibility in constructing nanosystems with different functions.
Hyaluronic acid		good cytocompatibility; good biodegradability; non-toxicity; high binding ability for tumor cell receptors including CD44, LYVE-1, RHAMM.
Dextran		great biocompatibility; excellent biodegradability; non-toxicity; alternative for PEGylation.
Alginate		good cytocompatibility; good biodegradability; mucoadhesiveness; versatile physicochemical properties for the addition of targeting moieties.

LYVE-1: lymphatic vessel endothelial-1 receptor; RHAMM: receptor for hyaluronic acid -mediated motility.

Table 2
Polysaccharide-based nanoparticles as delivery vehicles for cancer immunotherapy.

Polysaccharide Type	Nanomaterial	Loaded Agents	Therapeutic Effects	References
Chitosan	polyaniline-glycol-chitosan nanoparticles	R848	induce dendritic cell maturation,promote antitumor memory	[46]
	chitosan/poly (γ-glutamic acid) nanoparticles	interferon-γ	induce dendritic cell maturation and macrophage activation	[47]
	PEG = MT/PC nanoparticles	VEGF-siRNA, PIGF-siRNA	alter the microenvironment to be anti-tumoral	[48]
	mannose-chitosan-stearic acid nanomicelles	ovalbumin and CCR7 pDNA	induce dendritic cell maturation,increase $CD8^+$ T cell population	[49]
	poly (ethylene glycol)- g-chitosan hydrogel	therapeutic T cells	demonstrate a better antitumor efficacy of loaded T cells	[50]
Hyaluronic acid	HA-gold nanoparticles	ovalbumin	increase antigen presentation, induce $CD8^+$ T cell proliferation	[51]
	HA-paclitaxel-marimastat liposomes	HA-paclitaxel, marimastat	alter the tumor microenvironment to suppress tumor growth, metastasis and angiogenesis	[52]
	HA-based hydrogel	artificial T cell stimulating matrix	enhance activation of antitumor $CD8^+$ T cells	[53]
Dextran	pH-sensitive HA-dextran nanoparticles	PD-1 antibody, glucose oxidase	achieve a better therapeutic efficacy of PD-1 antibody	[54]
	spermine modified acetalated dextran nanoparticles	nutlin-3a, GM-CSF	induce dendritic cell maturation,increase $CD8^+$ T cell population	[55]
	dextran-grafted-poly (histidine) copolymer micell	BLZ-945	induce M1 macrophages,increase $CD8^+$ T cell population	[56]
	porous silicon@acetalated dextran@cancer cell membrane	exogenous antigen	induce dendritic cell maturation,promote Th-1 cell differentiation	[57]
Alginate	mannose-modified alginate nanoparticles	ovalbumin	increase tumor antigen presentation,induce $CD8^+$ T cell proliferation	[58]
Chondroitin sulfate	chondroitin sulfate-chlorin e6-lipoic acid nanoplatform	docetaxel	achieve chemo-sonodynamic combination therapy,induce tumor-associated antigen release,promote dendritic cell recognition,increase $CD8^+$ T cell population	[59]
Cyclodextrin	β-cyclodextrin-based covalent crosslinking nanoparticles	R848	induce M1 macrophages,suppress M2 macrophages	[60]

PEG: polyethylene glycol; MT: trimethyl chitosan; PC: citraconic anhydride grafted poly (allylamine hydrochloride); VEGF: vascular endothelial growth factor; PIGF: placental growth factor; HA: hyaluronic acid; PEI: poly (ethylenimine); GM-CSF: granulocyte-macrophage colony-stimulating factor; PD-L: programmed death ligand.

[77] and Elotuzumab [78]. Another immune modulating mechanism by antibodies is to block immune checkpoints. These immune checkpoints usually act as error correctors that prevent an overstressed immune system from harming healthy cells, but could also be utilized by tumor cells to escape immune elimination. By blocking tumor-related immune checkpoint proteins from binding their receptors or partner proteins, immune checkpoint inhibitors could effectively restore the immune function towards tumor cells and even promote an enhanced immune

Table 3
Polysaccharide-based nanoparticles with intrinsic immunomodulatory effects in cancer immunotherapy.

Polysaccharide Type	Nanomaterial	Therapeutic Effects	References
Chitosan	chitosan/poly (γ-glutamic acid) nanoparticles	stimulate M1 macrophages, promote dendritic cell maturation induce pro-inflammatory cytokines, increase antitumor T cell population	[61]
	chitosan conjugated green copper oxide nanoparticles	activate both Th1 and Th2 cells, induce pro-inflammatory cytokines, expand antitumor T cell population	[62]
Dextran	dextran-coated spermine functionalized dextran nanoparticles	promote dendritic cell maturation, stimulate M1 macrophage, induce pro-inflammatory cytokines	[63]
Herbal extract	gold-*Ganoderma lucidum* polysaccharide nanoparticles	induce dendritic cell maturation, increase antitumor T cells promote antitumor memory	[64]
	Ganoderma lucidum polysaccharide-conjugated bismuth sulfide nanoparticles	increase radiotherapy sensitivity, promote dendritic cell maturation, induce pro-inflammatory cytokines induce $CD8^+$ T cell proliferation	[65]
	Lepidium meyenii Walpers derived cationic polysaccharide	increase M1 macrophages	[66]

response. A cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blocker, ipilimumab, was the first immune checkpoint inhibitor approved by FDA for the treatment of cancer [79]. Due to safety concerns [80], programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) become the most safe checkpoints for new immunotherapeutic drugs. Nivolumab [81], Pembrolizumab [82], Atezolizumab [83], Avelumab [84], Durvalumab [85] and Cemiplimab [86] have been approved by FDA for the inhibition of PD-1 or PD-L1 to promote the immunotherapy of cancer. Cytokine therapy utilizes the immunomodulatory function of cytokines. Cytokines, such as interferons (IFNs) and interleukins (ILs, especially IL-2, IL-6, IL-12 and IL-15), are reported to be closely associated with antitumor immune responses, thus by administrating these cytokines externally, an enhanced antitumor activity could be achieved [87–91]. Currently, FDA-approved cytokines for cancer immunotherapy include IFN-α [92] and IL-2 [93]. IFN-γ has also been reported to be effective for cancer immunotherapy *in vitro* and *in vivo* [94], but no commercial IFN-γ drug has been approved.

Although the concept of cancer immunotherapy has been promoted for decades and immunotherapeutics have been approved for clinical practice, challenges still remain in this field and improvements are still actively pursued. One of the most important challenging issues is the off-target effect. Despite the fact that most of the approved immunotherapeutics have a targeting ability, the targeting efficiency is usually not quite high enough, leading to a decreased therapeutic efficacy and increased side effects [95–97].

2.2. Potential of polysaccharides and their derivatives for immune modulation

New immunotherapeutics are being developed to achieve a safer and more effective cancer immunotherapy. Among these immunotherapuetics, polysaccharides-based therapeutics stand out due to their easiness of production, preferable biocompatibility and most importantly, the effectiveness of modulating immune responses [98,99]. It has been discovered that polysaccharides could interact with the immune system to change the chemotactic factor and cytokine releasing status, maintain the balance between T helper (Th) type 1 and 2 cells, inhibit the expression of matrix metalloproteinase (MMP) and suppress the formation of tumor vessels [100]. Recent studies have also demonstrated that polysaccharides, especially botanical polysaccharides, could effectively induce the proliferation of macrophages and promote their phagocytic function towards foreign materials and tumor cells [101,102]. Polysaccharides and their derivatives that are produced from *Lepidium meyenii* or masson pine pollen could stimulate the release of pro-inflammatory cytokines/chemokines, reactive oxygen species (ROS) and nitric oxide (NO) from macrophages to result in an enhanced tumor immune [103,104]. In addition, it has been reported that polysaccharides from *Dendrobium devonianum*, *Atractylodis macrocephalae Koidz* and *Astragalus* could increase the proliferation of B cells and T cells, promote their differentiation into plasma cells and effector T cells, and induce their production of lymphocytic antibodies and cytokines to create a strong tumor immune reaction [105–107]. Studies also suggested that polysaccharides from *Rehmannia glutinosa* and *Pleurotus ferulae* have the ability to interact with NK cells and DCs to boost innate immune responses and regulate the adaptive responses [108–111]. Most of these immune stimulating effects from polysaccharides are believed to be realized through their recognition by receptors on immune cells like scavenger receptors and toll-like receptors (TLRs), members of the pattern recognition receptor (PRR) family [112–114]. Besides, polysaccharides can also be recognized by mannose receptors and Dctin-1, one of C-type lectin receptors (CLRs) that cooperate with TLRs in the initial inflammatory response, and the recognition could induce $CD4^+/CD8^+$ T cells-mediated adaptive Th17 and Tc17 immunities [115]. The recognition of polysaccharides by cell surface receptors may further trigger immune-enhancing pathways like NF-κB and p38 mitogen-activated protein kinase (MAPK) signaling pathways [116–118], leading to the induction of immune-related gene transcription, which results in the activation of immune cells and initiation of producing pro-inflammatory cytokines.

Although the effectiveness of immune stimulation by polysaccharides has been well-accepted, the relationship between polysaccharide structures and their immune stimulation function has not been unveiled. Studies have suggested that the conformation, molecular weight, presence of certain functional groups and branching degree of polysaccharides may be correlated with their immune stimulating performances [38]. It has been indicated that the conformation of polysaccharides could affect their interactions towards immune molecules or cells, thus influencing their immunomodulatory effects [119,120]. Molecular weight, as an important structural parameter for structure–function relationships, is also believed to significantly affect the immunological response of polysaccharides. For example, high-molecular-weight HA polymers have a very different immune response from smaller-molecular-weight HA oligomers [38]. More studies are needed to uncover this structure–function relationship. Furthermore, sulfation, carboxymethylation or phosphorylation of surface groups on polysaccharides and the addition of components like selenium have been reported to enhance or suppress the immune responses of polysaccharides [40,121,122]. Sulfation of polysaccharide

was reported to enhance the phagocytosis activity of macrophages and induce the release of pro-inflammatory cytokines [123]. This has been confirmed by *in vitro* and *in vivo* experiments [124,125]. Phosphorylation of polysaccharide surface groups is believed to enhance the proliferation of lymphocytes, induce the maturation of B cells and increase the ability of their antigen presentation and cytokines secretion, thus effectively regulating the systemic immune function [126]. The addition of selenium could promote lymphocyte proliferation, induce or promote lymphocytes to produce interferon, IL-2 and other soluble immune factors, which is supported by the study of Qin et al. [127]. However, the influence of carboxymethylation of polysaccharides on immunomodulation is quite dependent on the structure of the original polysaccharides. Studies have demonstrated that carboxymethylation of herbal polysaccharides from *Astragalus mongholicus* or the seeds of *Plantago asiatica* L. could effectively enhance the immune activity of immune cells such as DCs [109,128], while carboxymethylation of herbal polysaccharides from *Ganoderma atrum* [129] or *Dendrobium candidum* [40] had not enhanced the immune activity or had an immunosuppressive effect. Therefore, structure modifications of polysaccharides need to be rationally designed for favorable immunomodulatory effects.

When polysaccharides are applied as a drug delivery platform, the loaded immunotherapeutics should be aligned with the structure of their delivery platforms. For example, it was reported that positively-charged particles for gene delivery have higher transfection efficiencies compared with neutral or negatively-charged delivery vectors [130]. Therefore, chitosan, with a positive-charge property, has been applied to deliver nucleic acids for cancer immunotherapy more often than other polysaccharides like HA or dextran or alginate, which are negatively charged. The surface charge of polysaccharide-based nanomaterials should be considered when they are used to load polypeptide-based or protein-based antigens with different charges [131,132]. In addition, hydrophilicity or hydrophobicity of polysaccharides nanomaterials also plays a significant role in effectively loading and releasing immunotherapeutics [133,134]. By taking the above factors and commercial availability into consideration, chitosan, hyaluronic acid, dextran and alginate are the most widely applied polysaccharides in the immunotherapy. The structures of these polysaccharides are shown in Table 1 and their application as delivery vectors in cancer immunotherapy is summarized in Table 2. Although chitosan, hyaluronic acid, dextran and alginate without any modification are generally believed to have low/no immunogenicity, their derivatives are often reported to demonstrate excellent immunomodulatory effects with enhanced immune responses [40,135–138] as shown in Table 3. Thus, these polysaccharides have been widely employed to incorporate immunotherapeutic agents to prepare novel nanomedicines for cancer immunotherapy. Most of these polysaccharides-based nanomedicines could act as antitumor vaccines. They are distributed in lymph nodes after subcutaneous injection and target tumor-associated immune cells to achieve synergetic and enhanced cancer immunotherapy [41,139,140]. Some polysaccharides-based nanomedicines, especially HA-based nanomedicines with their binding ability towards CD44-expressing cells, could also target the tumor microenvironment to make tumor cells more vulnerable to immune responses [141,142].

3. Chitosan-based nanomedicines

Chitosan is a positively-charged natural polysaccharide that is derived from deacetylation of chitin, which is abundantly found in fungi cell walls and anthropods shells [143,144]. Chitosan is acid-soluble due to the amino groups of it possess an excellent protonation ability at a low pH environment, which could lead to preferred "pH-responsive manners" in acidic subcellular organelles such as endosomes and lysosomes. It had been reported that chitosan and their oligomers could interact with negatively-charged agents such as tripolyphosphate (TPP) to form a series of nanosystems with various particle sizes and zeta potentials [145]. Due to its versatility to form nanosystems with different functions, along with its excellent biocompatibility, non-toxicity and mucoadhesiveness for enhancing drug absorption and bioavailability, chitosan is usually considered to be one of the most widely used polysaccharides in the nanomedicine field [146–148]. The generated chitosan-based nanomedicines usually have high biodegradability, excellent biocompatibility, bioactivity and polycationicity [149–151], thus they are effective nanocarriers for drug delivery applications [152–154]. As will be presented next, only recently, there are several studies attempting to use chitosan-based nanomaterials to deliver immunotherapeutic agents for cancer treatment.

3.1. Chitosan-based nanosystems to deliver adjuvants

One of the most promising immunotherapeutic agents, which have been developed and also approved for clinical trials, are molecular adjuvants [155]. They enhance the efficiency of antigen delivery and induce their recognition by antigen presenting cells (APC). By increasing immunogenicity, adjuvants could stimulate the anti-tumor immunity and decrease the immune evasion of tumor cells. It has been reported that a few adjuvants could induce the expression of CD80 and CD86 on the surface of DCs, which are the markers of DC maturation. These maturated DCs would increase their production of pro-inflammatory cytokines that could boost downstream antitumor immune responses [156,157]. However, some adjuvants exhibit intrinsic immunogenicity thus they could be degraded before they achieve the modulatory effects towards DCs. Some adjuvants could systemically modulate the immune environment besides the maturation of DC, which would cause severe side effects [158,159]. How to effectively and selectively deliver adjuvants into DCs is crucial for adjuvant-based cancer immunotherapy. In this regard, Chen et al. [46] developed nanomedicines with hydrophilic glycol-chitosan (GCS) as the backbone and conjugated hydrophobic polyaniline (PANI) with GCS to address the above challenge. These PANI-GCS nanomaterials were utilized as a biocompatible and water soluble nanocarrier for successful delivery of resiquimod (R848), a TLR-7/8 agonist which has already been approved by FDA as an immunomodulatory agent for cancer clinical trials [160]. The PANI-GCS-R848 nanomedicines were found to promote their maturation selectivity towards DCs (Fig. 2a). The PANI moiety attached to the GCS backbone had excellent light absorption and great photothermal effect, while hydrophobic interaction and π-π stacking of PANI/R848 could enhance the loading efficiency of R848. These maturated DCs would secrete several pro-inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF)-α, which are actively involved in the immunity mediation and modulation of anti-tumor effects [161], in a considerable amount and for a prolonged time. A long-lasting memory of systemic anti-tumor responses was also observed from their experiments. These R848-loaded chitosan-based nanomedicines could be further systematically examined as in situ vaccines for cancer treatment. Another TLR-9 agonist CpG oligonucleotide has also drawn attention recently due to its excellent capability of maturating DCs [162,163].

Nevertheless, the majority of oligonucleotides was reported to be degraded by deoxyribonuclease (DNase) and excreted by the kidney rapidly after administration through injection subcutaneously, which significantly reduced their circulating time and the therapeutic dose, thus limiting their therapeutic applications [165,166]. To overcome this issue, chlorin e6 (Ce6)-doped-azobenzene-glycol chitosan (GC)-PEG--modified mesoporous silica nanoparticles (CAGE) were introduced to deliver CpG oligonucleotides (Fig. 2b) [164]. These CAGE nanoparticles were hypoxia-responsive and could protect the loaded oligonucleotide from biodegradation or renal clearance, thus improving the intracellular uptake efficacy as well as the targeting efficiency of adjuvants and photosensitizers to DCs. Since the delivered agents could induce the generation of immunogenic debris, promote the maturation of DCs, help exposure of tumor-associated antigens of tumor cells and enhance the antigen presenting effect of DCs, an increased intracellular uptake and

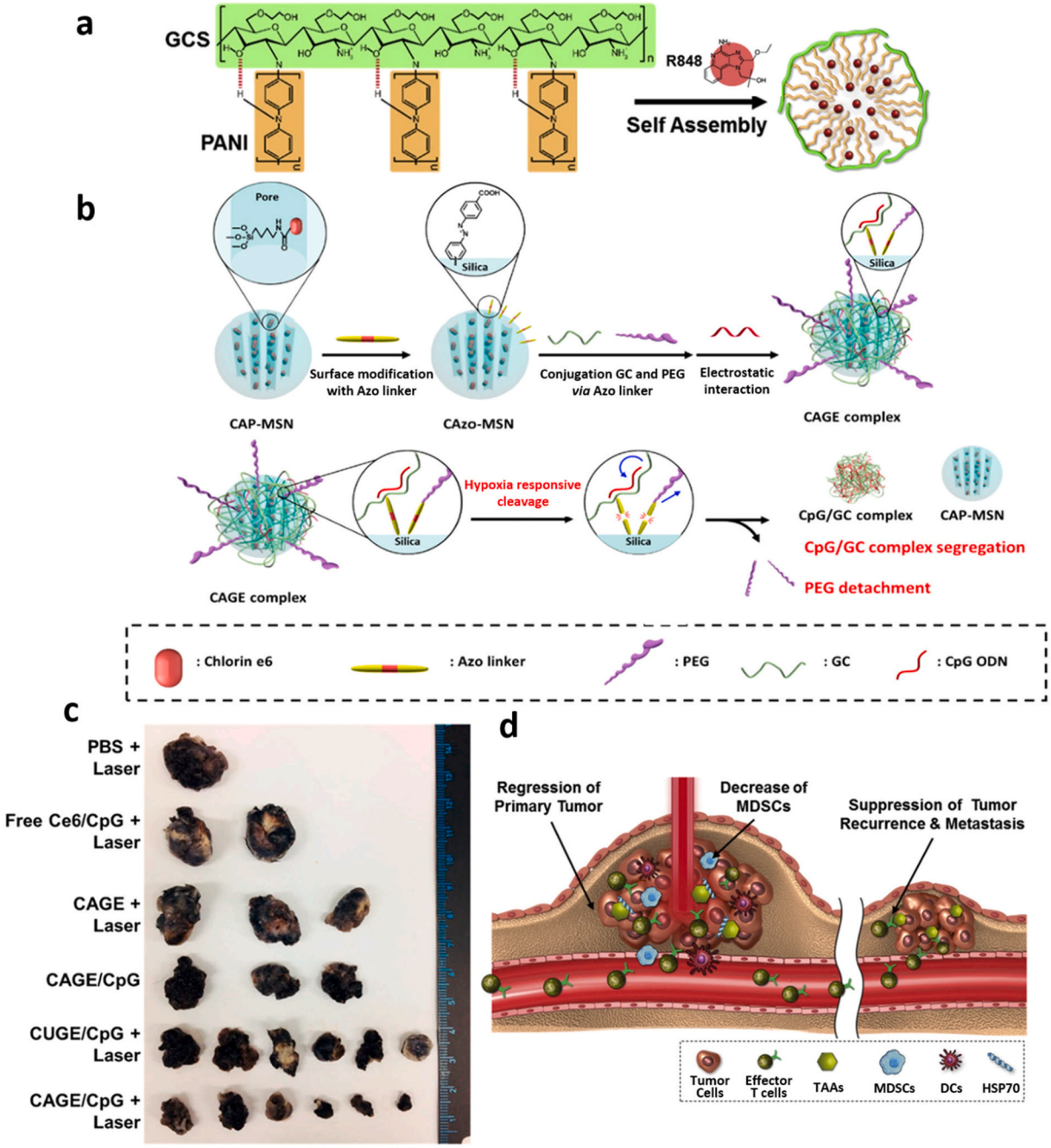


Fig. 2. Preparation of chitosan-based nanomedicines (a: R848@NPs; b: GC-CAGE complex) and their therapeutic application on cancer immunotherapy. The use of these chitosan-based nanosystems to carry immunotherapeutic agents could significant inhibit the tumor growth (c) thus beneficial for both primary and metastatic tumor treatment (d). Reproduced with permission from Refs. [46,164]. Copyright 2019 Elsevier and 2018 American Chemical Society, respectively.

targeting efficiency would result in a higher DC maturation rate and a greater antigen presenting efficiency, reduce the incidence of tumor evasion and promote a stronger immune response towards tumor cells. In addition to protective and targeting delivery of the loaded adjuvants, these chitosan-based nanomedicines could perform synergistically with photodynamic therapy to achieve multi-modality therapy of cancer. The PANI-GCS-R848 nanomedicines were reported to induce inhibition of tumor cell growth due to photo-generated hyperthermia and the immunoregulative effect from R848 [46], which enhanced the efficacy of these chitosan-based nanomedicines for cancer treatment.

3.2. Chitosan-based nanosystems to deliver cytokines

Another promising type of agents that are involved in immunotherapy of cancer is cytokines. Cytokines could direct proliferation, activation and differentiation of the downstream immune cells and induce them to express and secrete substances demonstrating tumor suppression or killing effects [167,168]. Chitosan-based nanoparticles have been explored for delivery of certain cytokines to achieve a better outcome of immunotherapy. Previous studies had demonstrated chitosan/poly (γ-glutamic acid) nanosystems and applied them to deliver therapeutic agents such as hormones and chemokines [169–171], and evaluated the maturation efficacy of their intrinsic macrophages and DCs [172]. Recently these chitosan/poly (γ-glutamic acid) nanosystems

had been further evaluated as a drug delivering platform to achieve targeting delivery of IFN-γ to DCs and macrophages [47]. They have discovered that these IFN-γ-loaded chitosan/poly (γ-glutamic acid) nanoparticles (IFN-γ-Ch/γ-PGA NPs) could increase the expression of CD40, CD83 and CD86 of DCs and human leukocyte antigen-DR (HLA-DR), and the secretion of pro-inflammatory cytokines such as IL-6, IL-12/IL-23 (p40) and TNF-α [173]. Administration of these IFN-γ-Ch/γ-PGA NPs resulted in promotion of maturation and activation of DCs. They also had a high internalization efficiency towards macrophages, thus they activated certain monocyte-macrophage lineages and increased the release of pro-inflammatory cytokines so as to enhance the immune stimulatory effect [174,175]. These Ch/γ-PGA NPs could not only protect the cytokines from degradation and retain their biofunctions, but also deliver therapeutic agents towards targeting macrophages and DCs so as to increase the therapeutic efficacy and decrease their side effects, which provided a new and effective way to promote cytokine-based cancer immunotherapy. While Ch/γ-PGA NPs worked well for delivery of IFN-γ, another study applied chitosan-modified selenium nanoparticles to successfully deliver TNF–α, another critical pro-inflammatory cytokine that could induce and activate downstream effectors for antitumor responses [176]. According to *in vitro* and *in vivo* results, these nanoparticles could achieve stable and sustained release of the loaded TNF-α derived polypeptides (P16) so that they could effectively suppress proliferation of several types of tumor cells, while demonstrated no toxic effect against normal non-tumorigenic epithelial cells. Since P16 was previously reported to exhibit a limited therapeutic efficacy due to its high renal clearance and hepatic metabolic rate [177], this nanoparticle-based delivery could prolong the circulating time of P16 and thus yielded a higher efficacy to affect the p38 MAPK/JNK signaling pathway, the G_0/G_1 cell cycle arrest, and the caspase-dependent apoptosis pathway so as to suppress proliferation and also induce apoptosis of tumor cells. It has been suggested that combination of multiple types of cytokines could achieve a synergistic immune effect, resulting in a better antitumor efficacy [168]. Chitosan-based nanosystems could be employed to deliver other types of cytokines or co-deliver multiple types of cytokines to enhance cancer immunotherapy.

3.3. Chitosan-based nanosystems to deliver nucleic acids

Apart from the delivery of the above discussed immunotherapeutic agents, chitosan-based nanomaterials are also explored to deliver nucleic acid (gene) for modulating immune responses for eradicating cancer. The immune responsive nucleic acid (DNA or RNA) could modify DCs or T cells genetically so that these genetically modified immune cells could enhance their responses to tumor antigens [178–180].

In a recent study, chitosan-coated selenium nanoparticles were prepared and conjugated with a folic acid-targeting moiety to deliver *Photinus pyralis* firefly luciferase (*Fluc*) mRNA [181]. These nanoparticles could efficiently bind and stabilize mRNA, protect them from degradation from RNase and selectively deliver them into cancer cells. More importantly, these nanomedicines possessed low cytotoxicity to normal cells but displayed much higher cytotoxicity to colorectal carcinoma (Caco-2) and colon carcinoma (HT-29) cancer cells, which significantly reduced the incidence of side effects, promoting a safer and effective way to deliver nucleic acids for cancer immunotherapy. However, the experimental data from these chitosan-coated nanomedicines were obtained at the cellular level and further evaluation of their *in vivo* delivery efficacy is still needed. Ali et al. [182] prepared PEG-chitosan-lactate nanoparticles to load therapeutic siRNAs. *In vitro* experiments demonstrated that these siRNA-loaded nanomedicines were low toxic, stable in serum and could achieve controllable release of the loaded siRNA within 60 h. Cellular and animal studies showed that these PEG-chitosan-lactate nanomedicines could selectively target T cells at the tumor site, enhanced T cell proliferation and reduced apoptosis. More importantly, they noticed that these siRNA-loaded nanomedicines could promote differentiation of T cells towards Th1 and suppress their differentiation towards regulatory T cells (Tregs). Since Th1 is one of main anti-tumor functioning T lymphocytes and the induction of Tregs is one of the mechanisms for immunosuppression and immune evasion of tumor cells [183–185], these siRNA-loaded PEG-chitosan-lactate nanomedicines could effectively stimulate anti-tumor immune responses selectively at the tumor sites without systemic injection of A2AR antagonists that may cause unwanted side effects through induction of Th1 and suppression of Tregs. As the induction of antitumor immune responses requires activation or inhibition of different receptors or signaling pathways, administration of multi-type nucleic acids targeting at different pathways may have the potential to further enhance the efficacy of cancer immunotherapy [186,187]. However, how to achieve co-delivery of different nucleic acids to targeting sites and simultaneously maintain their inherent bioactivity, is still a great challenge. Recently, chitosan-based nanomaterials have been used to address this challenge. A novel nanomaterial composing of polyethylene glycol and mannose-modified trimethyl chitosan (PEG = MT) and citraconic anhydride grafted poly (allylamine hydrochloride) (PC) was synthesized for co-delivery of both vascular endothelial growth factor (VEGF) siRNA (siVEGF) and placental growth factor (PIGF) siRNA (siPIGF) [48]. These serum stable and "smart" pH-sensitive nanomedicines could accumulate in tumor tissues and effectively target tumor-associated macrophages and breast cancer cells without damages to other normal cells. Two released siRNAs would synergize in effectively silencing certain genes, thus inhibiting proliferation of cancer cells and also changing the microenvironment of tumor tissues from pro-oncogenic to anti-tumoral. It is worth noting that, by co-delivery of two siRNAs using this nanomaterial, distant metastasis of the original tumor cells to lungs has also been significantly inhibited. Chitosan-based nanomaterials were also prepared to achieve co-delivery of not only nucleic acids, but a mixture of nucleic acids and therapeutic agents. For example, chitosan oligomers were mixed with TNF-α or CD40L plasmids to form DNA-loaded nanocomplexes [188]. Mammary carcinoma 4T1 cells were *in vitro* transfected with these chitosan-based nanomedicines and these transfected 4T1 cells could effectively induce the maturation of DCs and significantly increase the amount of pro-inflammatory cytokines secreted by DCs. This immune process would further stimulate the proliferation of T cells, enhance the production of IFN-γ while suppressing the release of IL-4 of these T cells, thus playing a more active role in the tumor immune response.

All the above studies indicated that the use of chitosan-based nanocomplexes could protect the integrity and increase the therapeutic efficacy of the loaded plasmids, while exhibiting low/no toxicity to normal cells. Since chitosan-based nanomaterials could also achieve targeting endocytosis to avoid the recognition of P-glycoproteins [189], using this nanomaterial to deliver therapeutic agents may also help the suppression of drug resistance. In addition to co-delivering cytokines and plasmids, these chitosan-based nanoparticles were applied to deliver CD40, inducible co-stimulator ligand (ICOSL), and EGFP-N1 mRNA to DCs to enhance the antitumor effects of these immune cells [190]. These mRNA-loaded chitosan nanocomplexes could induce a higher expression of CD40, ICOSL, CD86, and MHC-II on the surface of DCs, thus assisting in their maturation. The maturated DCs could promote the secretion of pro-inflammatory cytokines, which would further promote the proliferation of T cells and induction of Th1 differentiation that could strengthen the anti-tumor immunity [191]. These chitosan-based nanoparticles have demonstrated a high efficacy to deliver not only DNA or RNA, but also other different therapeutic agents to achieve synergistic effects between them and promote combinational therapy towards cancer treatment.

3.4. Chitosan-based nanosystems to deliver other types of immunotherapeutic agents

In addition to adjuvants, cytokines, and nucleic acids, there are other types of therapeutic drugs that could achieve the immunomodulatory effect for cancer treatment. Generally, cancer cells express a higher amount of tumor-associated antigens than normal cells, and some of these antigens are exclusively identified on tumor cells: tumor-specific antigens or neo-antigens [192,193]. But these antigens on tumor cells are usually not directly recognized by the immune system due to immune evasion of tumor cells [194], thus delivery of exogenous tumor-associated antigens into cancer cells is a feasible approach for anti-tumor immune stimulation. However, administration of these "naked" antigens alone would result in their premature degradation in the body fluid before they reach tumor sites. Concerns also arise that non-targeting administration of these antigens would cause undesirable systemic inflammatory reactions. Thus protective and selectively targeting delivery platforms are needed to promote antigen-based cancer immunotherapy [195,196]. Windberg et al. [197] applied polypeptide/Chit2DC (chitosan-deoxycholate) micelles to deliver an exogenous MAGE-3 polypeptide antigen, which is a $CD4^+$ and $CD8^+$ T cell epitope. In the animal model study, they demonstrated that these nanoscale vaccines could induce the immune response towards MAGE-3 expressing tumor cells by increasing differentiation of cytotoxic T lymphocyte (CTL) against MAGE-3 antigens, which would inhibit the growth of tumor cells and promote apoptosis in tumor tissues. Another mannose-chitosan-stearic acid nanomicelles have also been developed to deliver ovalbumin and CCR7 pDNA [49]. After these cargos-loaded nanomaterials were applied to the tumor-bearing mice, they could effectively promote the maturation of DCs and also induce the migration of these immune cells to lymph nodes to generate an enhanced antigen presenting process. A significant increase in the population of antitumor cytotoxic $CD8^+$ T cells had been witnessed. Both novel chitosan-based nanomaterials have achieved safe and effective delivery of exogenous antigens, and demonstrated the feasibility of applying tumor-associated antigens in cancer immunotherapy. It is worth noting that a patent [198] has already been applied in which chitosan nanoparticles were utilized to deliver antigens. Their patent document demonstrated that the chitosan-antigen complex nanoparticles possessed superior immune response-stimulating effects and could be used in therapeutic vaccination.

Rajaei et al. studied the immunoregulatory effect of arteether delivered by folic acid-chitosan-Fe_3O_4 composite nanoparticles [199]. These arteether-loaded chitosan-based nanomedicines were applied to 4T1 cell lines and breast cancer-bearing mice and significant augmentation in the production of cytokines IFN-γ and IL-4 was demonstrated. Since IFN-γ and IL-4 could induce and activate downstream antitumor effectors, the growth of 4T1 tumor cells was greatly inhibited and the tumor volume in the breast cancer-bearing mice was significantly shrunk. This experiment indicated that the folic acid-chitosan-Fe_3O_4 nanocomposite might be another promising arteether delivery platform for cancer immunotherapy. Another promising immunotherapeutic agent that could be used in cancer treatment is curcumin. It has been reported that curcumin could affect several cell signaling pathways that are involved in tumorigenesis and cancer metastasis and has the potential of converting Tregs into Th1 cells to avoid immune evasion of tumor cells and induce tumor killing responses [200–204], while the mechanism for the conversion is still unknown. One study has been conducted to use chitosan-based mesoporous silica nanoparticles [205] to deliver curcumin to promote the immunotherapeutic efficiency against cancer. Their *in vitro* results showed that these chitosan-based nanomedicines could effectively deliver curcumin and achieve stable and sustained controllable release of it in the U87MG glioblastoma tumor cells. Other studies also indicated that chitosan-based nanosystems could effectively deliver curcumin to tumor tissues thus increase their treatment efficacy in pancreatic cancer [206], colon cancer [207], cervical cancer [208], and breast cancer [209]. However, *in vivo* and clinical trials are highly demanded to confirm these immune enhancing effects towards cancer treatment. In addition to delivery of therapeutic drugs, chitosan-based polymers have also the potential to deliver living cells to achieve immunotherapy of cancer. Tsao et al. [50]designed poly (ethylene glycol)-g-chitosan hydrogel to carry therapeutic T cells. They found that the chitosan-based hydrogels were compatible with T cells and could retain their anti-tumor function. After loading T cells in the chitosan-based hydrogel, these T cells displayed a better therapeutic efficacy compared with controlled groups. It might be caused by the fact that these hydrogels could provide an optimal pore size to enable better invasion of T cells [210]. This study provides a new way of delivering T cells for immunotherapy of cancer but this method is still in need of further studies, for example, to unmasking the mechanism of action for better efficacy.

3.5. The immunomodulatory effect of chitosan-based nanosystems

Apart from delivery of immunotherapeutic agents, previous studies have demonstrated that chitosan-based nanosystems without therapeutic drugs could also have immunomodulatory properties. It has been reported that chitosan-based nanosystems could significantly increase the secretion of IFN-γ by Th1 cells and stimulate the cell-mediated immunity. Compared to chitosan oligosaccharides, the chitosan nanoparticles showed an enhanced immunomodulatory effect (1.2–1.5-fold), indicating the immunomodulatory effect could be tuned by aggregation of nanoparticles [211]. Wardani et al. [212] also applied chitosan nanoparticles to animal models and concluded that these nanoparticles could effectively stimulate immune responses and have a therapeutic potential for immunotherapy.

A further study [61] examined the detailed tumor immunity induced by chitosan-based nanosystems and it was found that they could stimulate macrophages towards a pro-inflammatory profile, expressing less CD163 molecules and producing more secretory IL-12 p40 and TNF-α. In addition, they discovered that these chitosan-based nanoparticles could stimulate DCs, increase their expression of co-stimulatory molecules and HLA-DR, promote the secretion of pro-inflammatory cytokines that could stimulate antitumor effectors, and induced differentiation and activation of $CD4^+$ and $CD8^+$ T cells so as to modulate the whole tumor immune response. Their *in vivo* study also confirmed these immunomodulatory results evidenced by inhibited growth of tumors and counteracted invasion of cancer cells. A more recent study [62] also achieved a similar immunostimulatory effect by application of chitosan-coated copper oxide nanoparticles. In both *in vitro* study on breast cancer cells (MCF-7) and cervical cancer cells (HeLa) and *in vivo* study on breast cancer (4 T1 cells induced) bearing mice, a great therapeutic efficacy of this nanomaterial has been demonstrated as it activated both Th1 and Th2 cells, increased the production of pro-inflammatory cytokines and expanded the $CD4^+$ T cell population. Furthermore, a chitosan-based biopolymer, N-dihydrogalactochitosan, could synergize with photodynamic therapy or cryoablation therapy to result in better antitumor efficacy. This synergetic effect of N-dihydrogalactochitosan was further confirmed by its ability of direct tumor killing and prominent immune modulation [213]. More recently, another chitosan micelle has been synthesized as antigen-capturing adjuvants that could achieve an enhanced cancer immunity. It has been discovered that this chitosan-based nanomedicine could effective target at tumor-draining lymph nodes and induce strong $CD4^+$ and $CD8^+$ T cell antitumor responses [115,214]. Based on previous positive findings, Moran et al. [215] published a review to systemically examine the immunomodulatory properties of chitosan polymers. In their review, they concluded that chitosan-based materials could activate both cGAS-STING DNA sensing pathway and NLRP3 inflammasomes so as to induce differentiation and activation of Th1 cells and suggested they could be applied as a promising vaccine adjuvant for cancer immunotherapy.

Overall, chitosan-based nanomaterials have great potential to use in

the immunotherapy of cancer. These nanomaterials could not only act as a nano-platform to carry immunotherapeutic agents to tumor tissues effectively and selectively so as to enhance anti-tumor immune responses, but also display immunomodulatory effects as immune adjuvants themselves to induce tumor-killing immune responses. Despite positive outcomes of their *in vitro* and *in vivo* studies, clinical trials are required to examine *in vivo* safety and effectiveness of these chitosan-based nanomaterials as potential immuno-therapeutics towards cancer treatment.

4. Hyaluronic acid-based nanomedicines

HA is negatively charged natural polysaccharides and they have been widely used in the biological and medicinal field. It has a linear structure with repeated units of N-acetyl-D-glucosamine and D-glucuronic acid disaccharide bound via beta-linkages [216]. The hydroxyl, carboxylic and N-acetyl groups of HA allow further structural manipulation via chemical reaction, which opens a door for broad applications of this material [217]. Similar to chitosan, HA is a natural biomaterial that could be found in many living organisms. HA is one of the main components of the extracellular matrix, which are synthesized and secreted by interstitial cells such as fibroblasts [218]. While low-molecular-weight HA oligomers resulting from degradation by hyaluronidase was reported to be immunostimulatory [214,219], HA polymers with a high molecular weight have been demonstrated to possess great cytocompatibility and biodegradability, low toxicity and no immunogenicity. Thus many studies have been conducted to develop HA-based medicines for biomedical applications [220,221]. Many cancer cells overexpress CD44, lymphatic vessel endothelial (LYVE)-1 receptors and receptor for HA-mediated motility (RHAMM), which are HA-binding receptors [141,222], hence one approach to utilizing HA is to apply HA-based nanomaterials as drug delivery carriers to selectively target tumor cells [223–225]. Recently, the HA nanosystem-based targeting drug delivery system has been developed for cancer immunotherapy.

4.1. Hyaluronic acid to induce immunoprotection

Although immunotherapy of cancer diseases requires stimulation of patients' immune responses so that certain immune cells such as DCs, T cells and macrophages could be activated and maturated to present tumor killing properties and to produce pro-inflammatory cytokines [226,227], immunotherapeutic drugs themselves are exogenous antigenic agents that could be recognized and eliminated by immune systems before they reach tumor cells. That is partially the reason why managing these immunotherapeutic agents alone usually results in a limited efficacy and often leads to unfavorable side effects [228–230]. HA, on the other hand, is a polysaccharide that demonstrates an anti-inflammatory and anti-immunogenic function. It has been reported that HA could provide an immunoprotective and immunomodulatory effect towards conjugated/encapsulated agents and protect them from elimination by the immune system [137,231,232]. Although this anti-inflammatory effect of HA may seem to be contradictory to the principles of immunotherapy, this effect results in a decrease in the incidence of premature degradation of loaded drugs and a reduction in undesired immune responses. Since HA could selectively target CD44, LYVE-1 and RHAMM receptors that are usually overexpressed by tumor cells, HA-assisted delivery of exogenous immunotherapeutic drugs would increase their accumulation inside tumor tissues and selectively stimulate immune responses in the tumor microenvironment. Likewise, HA could directly target some immune cells through CD44 targeting/binding [233]. HA, often as a subset to bind to CD44 on T cells (mouse), could inducibly stimulate PMA/ionomycin, CD3 antibodies and specific antigens [234]. HA could also bind to $CD4^+$ $CD25^+$ T regulatory cells (human and mouse) and stimulate $CD3^{+/-}$CD28 activation [235]. These processes would result in an increased efficacy of loaded immunotherapeutic drugs and decreased incidence of side effects (Fig. 3).

4.2. Hyaluronic acid-based nanosystems to deliver tumor-associated antigens

Using HA-based nanosystems to deliver tumor-associated antigens to enhance the immunity towards tumor cells is one of the most promising applications of HA-based nanoparticles for cancer immunotherapy. The use of HA-based nanomaterials was reported to extend the release profile of administrated immunomodulatory agents, thus effectively enhancing their therapeutic efficacy [237]. Although several tumor-associated antigens [238,239] are helpful in cancer

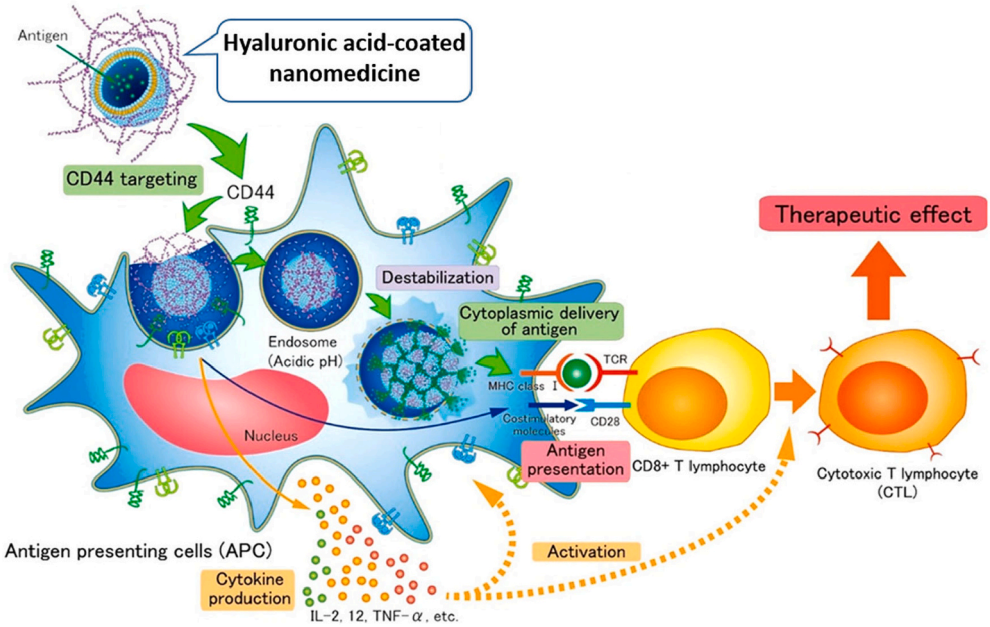


Fig. 3. Hyaluronic acid-coated nanomedicines could selectively target at $CD44^+$ cells, effectively deliver loaded drugs into the cytoplasm and promote the activation of antigen presenting cells. Reproduced with permission from Ref. [236]. Copyright 2019 American Chemical Society.

immunotherapy, ovalbumin (OVA) is the most widely used one due to its bioavailability and therapeutic efficacy [240,241]. However, similar to other soluble antigens, administrating OVA alone usually does not result in a satisfactory therapeutic effect. This is mostly caused by its intrinsic immunogenicity and an insufficient dose delivered into immune cells. Thus it is important to develop delivery platforms to aid in *in vivo* delivery of these tumor-associated antigens [242]. Recently, a novel multifunctional micellar platform, consisting of self-assembled polyethylenimine (PEI), vitamin E succinate (VES), HA and PEGylated HA (mPEG-*g*-HA), was introduced to load OVA to form immunotherapeutic nano-micelles (OVA@mPEG-g-HA/VES-g-PEI) [243] (Fig. 4). It has been discovered that HA in these micelles could decrease the cytotoxicity of the attached PEI by neutralizing its positive charge and also assist in the targeting delivery of the nanomedicines into HA receptor-overexpressed tumor cells. This HA receptor-targeted delivery would further increase cellular uptake of the micelles into tumor cells. Once this endocytosis process is completed, hyaluronidases would degrade the HA shell of the micelles so as to expose the inner OVA-loaded PEI structures. This process could also benefit for the endosome/lysosome-mediated OVA release and then promote antigen presentation. These OVA@mPEG-g-HA/VES-g-PEI-treated tumor cells could express MHC-I peptide epitope $OVA_{257–264}$ on their surfaces so that DCs could recognize and then trigger differentiation and activation of antigen-specific $CD8^+$ T cells to achieve the tumor killing responses [243].

However, although these HA-based micelles could promote the anti-tumor immunity, this immune stimulatory effect does not last longer, and the long-term immune enhancement is still relatively weak [244,245]. Thus future modification of these micelles is needed to extend the stimulatory time. Interestingly, another PEI-derived nanoparticles have also been adopted to deliver therapeutic agents. Instead of HA, these nanoparticles were combined with HAase to break down extracellular HA so as to increase the permeability of these nanoparticles to tumor tissues [246]. Using this method, these PEI-HAase nanomaterials could successfully deliver both OVA and CpG to induce a better efficacy of immunotherapy. This method sacrifices the targeting ability of HA but utilizes the penetrating ability of HAase to achieve enhanced intracellular uptake and a sufficient amount of therapeutic agents in tumor site. This concept has also been applied in another study [247]. However, further examinations are required to elucidate which method, HA or HAase-assisted delivery, could achieve a better immunotherapeutic efficacy.

Besides HA (ase)-PEI nanosystems, nanosystems made from HA, OVA and gold (Au) particles have also been applied for immunotherapy [51] (Fig. 5). It has been reported that after triggering with laser irradiation, these nanomaterials could achieve a similar immune stimulation process to enhance the tumor immunity. During this process, near infrared (NIR) laser irradiation could trigger not only the rupture of endosomes and lysosomes, but also the production of ROS which could enhance the proteasome activity and boost the antigen presenting process [248]. Moreover, these loaded OVA and NIR irradiation generated ROS could promote the enhancement in $CD8^+$ T cells-mediated anti-tumor immune responses, endowing this HA-Au nanomaterial as an excellent platform candidate to boost antitumor immunity, but ensure the targeting delivery of antigens with negligible toxicity. Alternatively, pH-sensitive HA derivative-modified liposomes have been developed to achieve targeted delivery of exogenous antigens to DCs [236]. These antigen-loaded nanomaterials could increase the production of anti-tumor cytokines by Th1 cells and induce strong anti-tumor responses, leading to effective tumor growth inhibition in the tumor-bearing mice.

Although above studies have explored the use of HA-based nanosystems to deliver sole antigens, a recent study [249] attempted to employ levodopa and poly (ε-caprolactone-*co*-lactide)ester-functionalized HA hydrogels to co-deliver both OVA and granulocyte–macrophage

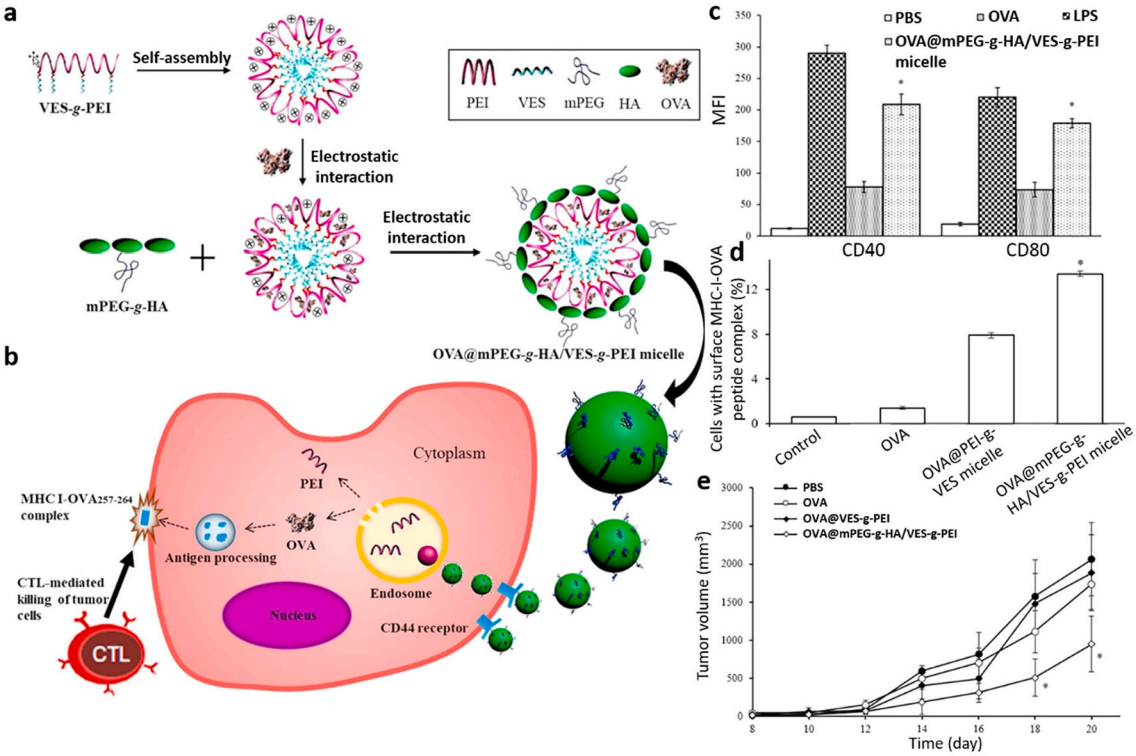


Fig. 4. Synthesis of OVA-loaded mPEG-g-HA/VES-g-PEI micelle (a) its therapeutic efficacy on cancer immunotherapy. This antigen loaded HA-based nanomedicine could targetedly deliver OVA into the tumor cells and induce an enhanced cytotoxic T lymphocyte (CTL)-mediated immune response (b). This HA-based nanomedicine could effectively induce the maturation of DCs (c) and increase the expression of tumor-associated antigens to activate CTLs (d), thus killing tumor cells (e). $^*p < 0.01$ compared with the OVA group in (c) and (d); $^*p < 0.01$ compared with all other groups in (e). Reproduced with permission from Ref. [243], Copyright 2019 Elsevier.

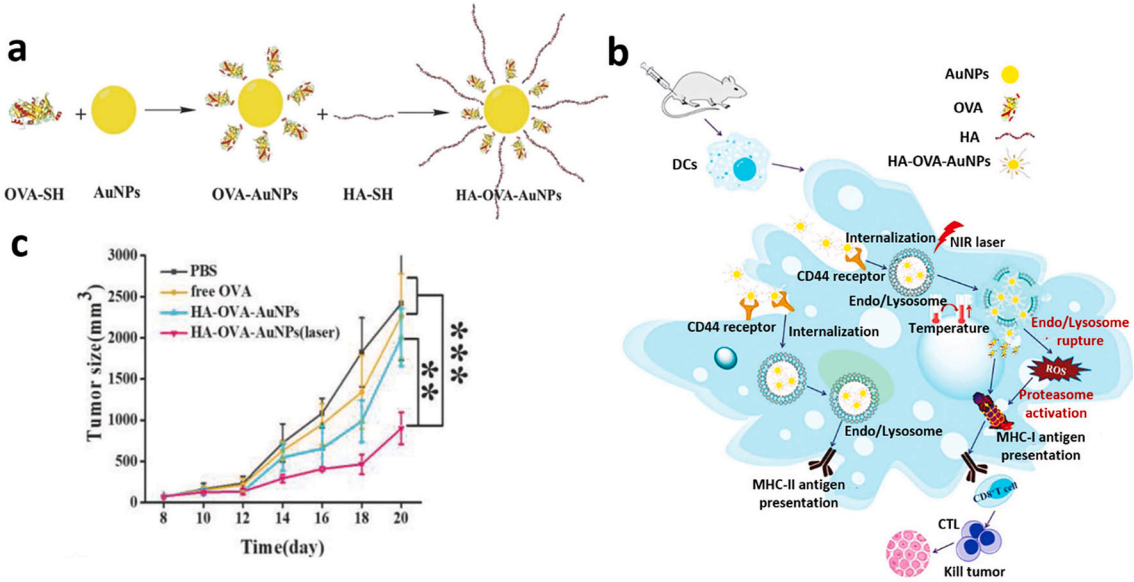


Fig. 5. Synthesis of HA-OVA-AuNPs complexes (a) and its therapeutic efficacy on cancer immunotherapy. This HA-based nanoparticle could be used as nanovaccine and effectively enhance both MHC-I and MHC-II antigen presentation process (b), thus demonstrating a comprehensive anti-tumor immune promoting ability to significantly inhibit the tumor growth (c). $^{**}p < 0.01$; $^{***}p < 0.001$. Reproduced with permission from Ref. [51]. Copyright 2018 WILEY-VCH Verlag GmbH & Co. KGaA.

colony-stimulating factor (GM-CSF). The stable release of the loaded drugs from the hydrogels suppressed the growth of tumor cells. It is worth noting that subcutaneous injection was utilized as the administration route, which could effectively avoid potential side effects due to systemic drug administration. The HA-based nanomaterials were also employed to deliver antigens in a needle-free administration route. Bussio et al. [250] found that OVA-loaded HA nanovaccines could be absorbed through skin thus no needles were involved in this process to avoid risks of injuries and infections. However, more studies are needed to confirm the *in vivo* therapeutic efficacy of the HA-based nanovaccines through this needle-free approach.

4.3. Hyaluronic acid-based nanosystems to deliver other immunotherapeutic agents

Besides tumor-associated antigens, HA-based nanosystems have also been employed for delivering other types of therapeutic agents to promote immunotherapy of cancer diseases.

CpG oligodeoxynucleotide (CpG ODN) and polyinosinic-polycytidylic acid (Poly I: C) are both members of pathogen-associated molecule pattern (PAMP) families that could be recognized by TLR-9 and -3. The former is usually found in bacteria and the latter is a synthetic analogue of double-stranded RNAs from viral-infected mammalian cells [251–254]. The combination of these two substances was reported to demonstrate synergistic effects to stimulate T cell responses and thus were explored as promising immune adjuvants for immunotherapeutic vaccines [255,256]. Despite their effectiveness, this combination would result in severe side effects. Using phosphorothioate to modify the phosphodiester backbone could be one possible solution, but this solution would inevitably increase the cost for this therapy. Liu et al. [257] developed HA-modified cationic lipid-poly (lactic-*co*-glycolic acid) (PLGA) hybrid nanoparticles to deliver both Poly I:C and natural phosphodiester CpG ODNs. They discovered that these adjuvant-loaded nanomedicines could significantly induce the maturation of DCs and increase the population of antitumor $CD4^{+}IFN\text{-}\gamma^{+}$, $CD8^{+}IFN\text{-}\gamma^{+}$ and $CD8^{+}CD107a^{+}$ T cells, while inhibiting the development of immunosuppressive myeloid-derived suppressors cells. Furthermore, they found these adjuvant-loaded nanomedicines could increase the population of memory $CD4^{+}$ and cytotoxic T cells and shorten the intervals of these memory T cells to secret antitumor IFN-γ when encountered with specific antigens. Importantly, this inexpensive HA nanoparticle-based delivery system could enhance the bioavailability of CpG ODNs and reduce the risk of side effects caused by positively-charged cationic lipids, which made these adjuvant-loaded nanomedicines safer and more affordable for cancer immunotherapy. In addition to delivering CpG ODN with Poly I: C, in another recent study [258], HA-based nanoparticles were employed to load CpG along with another therapeutic hypoxia inducible factor: signaling inhibitor Acriflavine (ACF) [259–261]. In this study, HA coated metal–organic framework-based nanoparticles were synthesized through H2TCPP and zirconium ions as a delivery platform (PCN-ACF-CpG@HA). Due to the binding ability of HA, these PCN-ACF-CpG@HA could selectively target cancer cells which usually overexpress CD44 receptors. The synergistic therapeutic effect of the loaded CpG and ACF has been demonstrated by inducing significant antitumor immune responses and inhibiting growth and metastasis of tumor mass. This opens a new avenue to using HA-based nanomedicines for cancer immunotherapy at a low cost.

Although chemotherapy and immunotherapy are two different methods for cancer treatment, different types of therapeutic agents with distinct antitumor mechanisms could be combined to achieve a greater tumor inhibition efficacy. Nevertheless, co-delivery of different types of therapeutic agents together and maintenance of their own biofunctions remains a challenge. Lv et al. [52] used HA-based nanoparticles to deliver both chemotherapeutic and immunotherapeutic agents to achieve a combinational therapy. They used a HA-paclitaxel (HA-PTX) prodrug and marimastat (MATT)-loaded thermosensitive liposomes (MATT-LTSLs) to from self-assembled nanoparticles and applied them to the treatment of breast cancer. The results showed that these CD44-targeting nanomedicines could selectively deliver the loaded drugs (HA-PTX and MATT) into the tumor microenvironment, inhibit the matrix metalloproteinase (MMP) and expression of TGFes and TNC, and suppress tumor growth, metastasis and angiogenesis. This provides another effective way to promote the nanomaterial-based combination cancer therapy. Camptothecin (CPT) is a chemotherapy drug that suppresses the activity of DNA enzyme topoisomerase I in tumor cells so as to achieve remarkable inhibition effect against tumor cells [262,263]. Sun et al. [264] found that CPT-conjugated HA nanomedicines could have synergistic effects to increase the immunotherapeutic efficacy.

Although 4T1 tumor cells usually express a low level of PD-L1 and they do not have great response to the anti-PD-L1 therapy, these CPT-conjugated HA nanomedicines could sensitize the tumor microenvironment so as to enhance the immune checkpoint blockade therapy. The effect of improving the sensitivity of the tumor microenvironment to immunotherapeutic drugs by a chemotherapeutic agent was also confirmed from previous combinational therapeutic studies [265–267]. It is believed that the incorporation of chemotherapeutic agents could enhance the proliferation of long-term and effective tumor antigen–specific T lymphocytes, thus achieving a synergic antitumor efficacy from chemotherapy and immunotherapy [268,269]. However, the detailed mechanisms remain to be discovered.

Herbal extracts such as curcumin and baicalin are another type of potential immunotherapeutic agents, which had been delivered by using HA-derived nanoparticles delivery platforms to achieve effective cancer chemotherapy [270–273]. Recently, the HA-based nanoparticles were employed to deliver herbal extracts so as to promote cancer immunotherapy. Wang et al. [274] developed quercetin-dithiodipropionic acid-oligomeric hyaluronic acid-mannose-ferulic acid (Que-S-S-oHA-Man-FA, QHMF) to form dandelion-like nanomicelles for delivering both curcumin and baicalin into tumor tissues. They demonstrated that these drug-loaded nanomicelles could easily penetrate through vascular barriers and enter tumor tissues. Further examinations revealed that these drug-loaded nanomicelles could reprogram the tumor-associated macrophages from a pro-tumor M2 phenotype into a tumor-killing M1 phenotype, thus exhibiting a higher tumor growth inhibition effect compared with free curcumin and baicalin. Moreover, increasing secretion of cytokines TNF-α and IL-6 indicated that baicalin could be employed as an adjuvant to enhance the immunomodulatory efficacy. Recently, hyaluronate-polylactide (HA-PLA) nanoparticles have also been applied to encapsulate curcumin [275]. Instead of promoting antitumor immunity, these drug-loaded nanomedicines could reprogram macrophages from a M1 phenotype to a M2 phenotype so as to reduce the production of pro-inflammatory cytokines and suppress the inflammation response. Although some studies stated that curcumin could promote inflammatory immune responses towards cancer [276,277], curcumin has also been widely used in the treatment of autoimmune diseases which rely on the inflammatory immune inhibition effect of curcumin [278–280]. Thus the therapeutic mechanism of action of these curcumin-loaded HA-based nanomedicines for tumor immune responses still remains controversial.

Besides the above-mentioned therapeutic agents, a US patent document [281] reported HA-based layer-by-layer nanoparticles to load cytokines for the treatment of cancer. The proposed nanosystems were composed of a liposomal core, a bilayer poly (L-arginine) coating and an HA and poly (L-glutamic acid) polymer coating. These nanoparticles were applied to encapsulate and deliver cytokines such as IL-12 and found that this cytokine-loaded nanomedicine formulation could significantly increase the secretion of antitumor IFN-γ by splenocytes, and the tumor growth of both MC38 tumor-bearing and HM1 tumor-bearing mice had been effectively suppressed. However, although cytokines have been greatly appreciated in cancer immunotherapy [168], the strategy of using HA-containing nanoparticles to deliver cytokines to enhance the immunotherapy efficacy directly is still at the early stage. Recently HA-based hydrogels were developed to deliver artificial T cell stimulating matrix, which is not cytokines but a mixture of substances (ECM, Anti-CD28, MHC, etc) crucial for T cell activation. Antitumor immune responses stimulation was achieved [53]. Further investigations are needed to evaluate the efficacy and clinical applicability of this immunotherapy method.

Overall, HA-based nanosystems, with their selective targeting ability to tumor cell receptors and their immunoprotective effects to protect the conjugated/enveloped therapeutic agents, provide a simple and effective way to deliver exogenous drugs with minimal side and toxic effects, which makes them a very promising candidate for delivery of immunotherapeutic agents towards cancer immunotherapy. With a deep understanding of tumor immunity and the emergence of new therapeutic concepts and new immunotherapeutic drugs, more applications of HA-based nanomedicines for cancer immunotherapy will be further discovered and evaluated.

5. Dextran-based nanomedicines

Dextran is a polysaccharide with an α-1,6-glycosidic bonding chain. It is water-soluble with great biocompatibility and biodegradability and has low toxicity and non-immunogenicity. Modifications of dextran through the hydroxyl groups in the backbone chain would allow interactions with selective receptors and other therapeutic ligands or agents, and remain their biocompatibility, which makes it another excellent candidate for nano-delivery of therapeutic drugs to achieve efficient treatment of diseases [282–285]. Furthermore, it has been indicated that dextran could be utilized as an alternative for PEGylation to prevent interactions of nanomedicines with opsonin [147,286]. Due to these advantages of dextran, it is widely used for the formation of nanomedicines. Recently, a number of dextran-based nanomedicines have been developed for cancer immunotherapy.

5.1. Dextran-based nanosystems to deliver immunotherapeutic agents

Wang et al. [54] developed a microneedle patch to deliver anti-PD-1 antibody into tumor tissues to achieve immunomodulation (Fig. 6). In their study, the microneedle patch consisted of biocompatible HA and pH-sensitive, anti-PD-1 and glucose oxidase-loaded dextran nanoparticles. The drug-loaded nanoformulations were applied to the treatment of melanoma in model mice. The microneedle patch could effectively deliver PD-1 antibodies into the tumor microenvironment and achieve sustained release of them. They discovered that the therapeutic efficacy of this delivering strategy was greater than that of administrating free anti-PD-1 antibodies. This microneedle patch-assisted immunotherapy enhancement technology has already been filed as a patent by this research group [287]. Another immunotherapeutic agent (type B CpG DNAs) has been conjugated to dextran polymers and the formulated nanomedicines were applied to tumor-bearing mice [288] (Fig. 7a). These dextran-CpG conjugates were discovered to significantly enhance the antigen presenting process and increase the population of $CD8^+$ T cells to achieve improved tumor killing immune responses. Yuba et al. [289] suggested that dextran and its derivatives could be added to construct pH-sensitive liposomes that could increase the safety and efficacy of the delivered antigens. More recently, Shin et al. [290] introduced a carboxymethyl dextran (CMD)-based polymeric conjugate to deliver exogenous antigens (Fig. 7b). Ovalbumin (OVA) was loaded into this polymeric conjugate with CMD as the backbone. This drug-loaded nanomaterial was applied to tumor-bearing mice. Compared with free OVA, this CMD-OVA conjugate could target tumor tissues and accumulate there with a prolonged retention period, effectively promoting the antigen presentation process and stimulating greater anti-tumor immune responses. In addition to these immunotherapy strategies, a few studies on dextran-based nanosystems have been attempted to deliver therapeutic agents to achieve reprogramming of tumor-associated macrophages. In a recent study conducted by Wang et al. [56], they synthesized a novel erythrocyte-cancer cell hybrid membrane camouflaged pH-responsive dextran-grafted-poly (histidine) copolymer micelle to deliver BLZ-945, a CSF-1R inhibitor specific for tumor-associated macrophages. Their preclinical results showed that this nanomedicine could effectively reprogram the tumor microenvironment with increased M1 macrophages and elevated $CD8^+$ T cells, thus resulting in inhibition of tumor growth. Besides, dextran-based nanomaterials have M2-TAMs targeting ability. Huang et al. developed a dextran-based tumor-targeting nucleic acid delivery system derived from a tumor microenvironment-responsive carrier and a TAMs-specific receptor [291]. All these recent studies demonstrated dextran-based

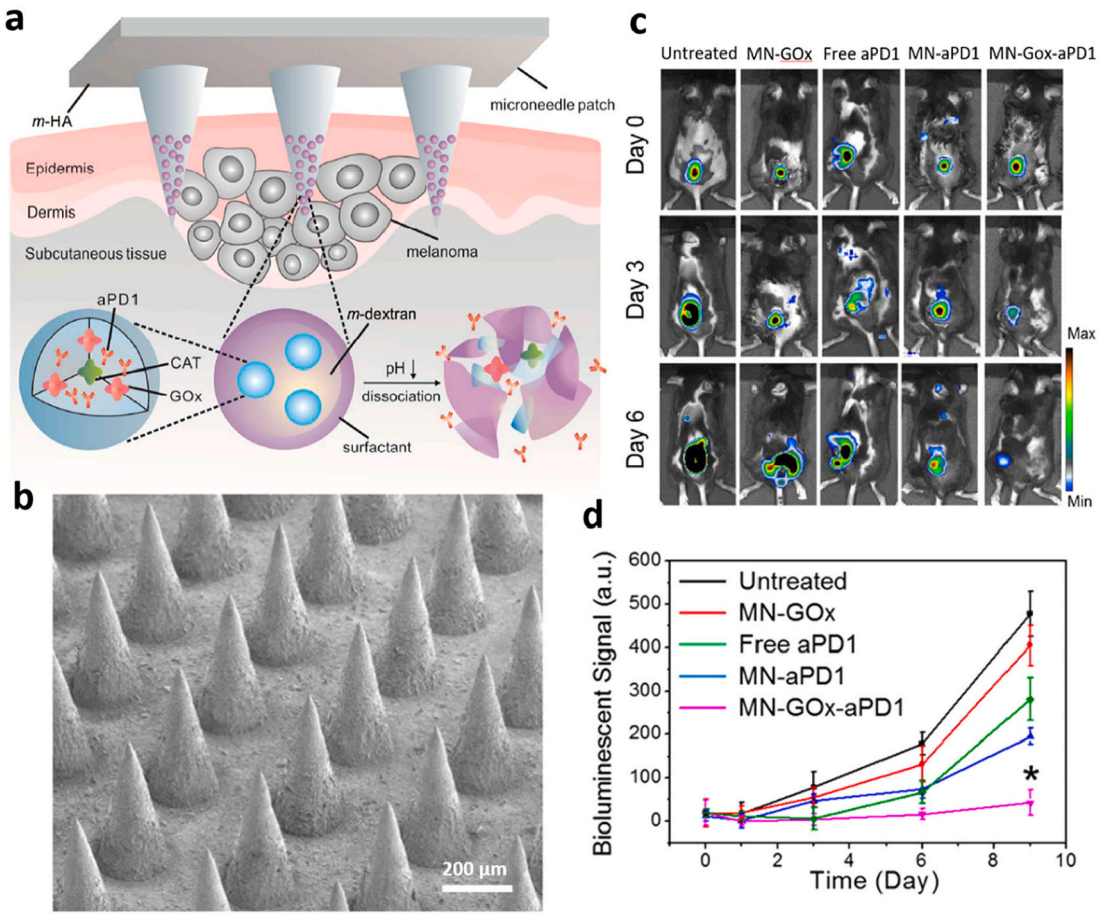


Fig. 6. The structure of anti-PD-1therapeutics loaded dextran-based nanoneedle patch MN-Gox-aPD1 (a: Schematic diagram; b: SEM image) and its therapeutic efficacy on cancer immunotherapy. This nanoneedle patch could effectively inhibit the growth of tumor tissues and reduce the tumor size, resulting in a decreased tumor signal in bioluminescence imaging *in vivo* (c, d). $*p < 0.05$. Reproduced with permission from Ref. [54]. Copyright 2016 American Chemical Society.

nanomaterials as an excellent candidate for targeting delivery of various immunotherapeutic agents with low apparent toxicity. On the basis of these positive results, further studies could be conducted to optimize the structure of these dextran-based nanomaterials for delivering different therapeutic agents to achieve a combinational therapy with better outcomes. In this context, Bauleth-Ramos et al. [55] used spermine-modified acetalated dextran nanosystems for co-delivery of *cis*-imidazoline nutlin-3a, a chemotherapeutic agent, and cytokine GM-CSF, an immunotherapeutic agent. These dextran-based nanomedicines could release the loaded cargos in a pH-dependent manner and also help in promoting endosomal/lysosomal escape of the delivered drugs. Their *in vitro* study revealed that these nanomedicines could selectively target wild-type p53 cancer cells and exhibit killing effects on them, but displayed no toxicity to immune cells. These nanomedicines could also maturate DCs by increasing the expression of CD83 and CD86 on their surfaces, which would enhance their antigen presenting abilities, induce proliferation and activation of the down-stream immune cells like cytotoxic $CD8^+$ T cells, promote the secretion of IL-1β and reduce the expression of IL-10. Based on these findings, acetalated dextran nanoparticles-loaded injectable alginate cryogel was also introduced as an in situ cancer vaccine [292]. This peritumoral injectable cancer vaccine was reported to demonstrate cytotoxicity towards tumor cells and induce immunogenic cell death, which potentially decreased cancer recurrence.

5.2. The immunostimulatory effects of dextran-based nanosystems

In addition to their drug delivering ability, previous studies also demonstrated the intrinsic immune stimulating properties of dextran-based nanosystems. Fontana et al. designed porous silicon@acetalated dextran@cancer cell membrane (TOPSi@AcDEX@CCM) nanovaccines for immunotherapy of cancer [57]. In their study, thermally-oxidized porous silicon was coated by acetalated dextran polymers and the nanostructure was co-extruded with cancer cell membrane particles to form core-shell-structured nanovaccines. These nanovaccines could significantly increase the expression of CD80 and CD86 on antigen presenting cells and induce T cells activation on both KG1 and BDCM cells, which could result in a greater immunostimulation efficacy. In addition, the authors noticed that these nanovaccines could induce the polarization of T cells towards Th1 cells to secret a greater amount of anti-tumor IFN-γ and IL-2 as well. Furthermore, this nanovaccine system could also be used to deliver exogenous antigens such as Trp2 to further improve the immunotherapeutic efficacy [57]. Moreover, Bamberger and their colleagues [63] developed a linear low molecular-weight dextran attached with spermine-modified acetalated dextran nanoparticles. These surface-modified dextran nanosystems could selectively target DCs and trigger the activating signaling pathways of DCs, which could significantly stimulate activation of these antigen presenting cells. A similar immunostimulatory effect was also found for B cells and macrophages [63,293,294]. However, in this study, it was also indicated that these dextran-based nanoparticles would induce cytotoxic effects on immune cells, which is the main drawback of applying them for cancer immunotherapy. Further studies are needed to reduce the cytotoxicity of these dextran-based nanosystems to immune cells and discover more clinical applications for cancer immunotherapy.

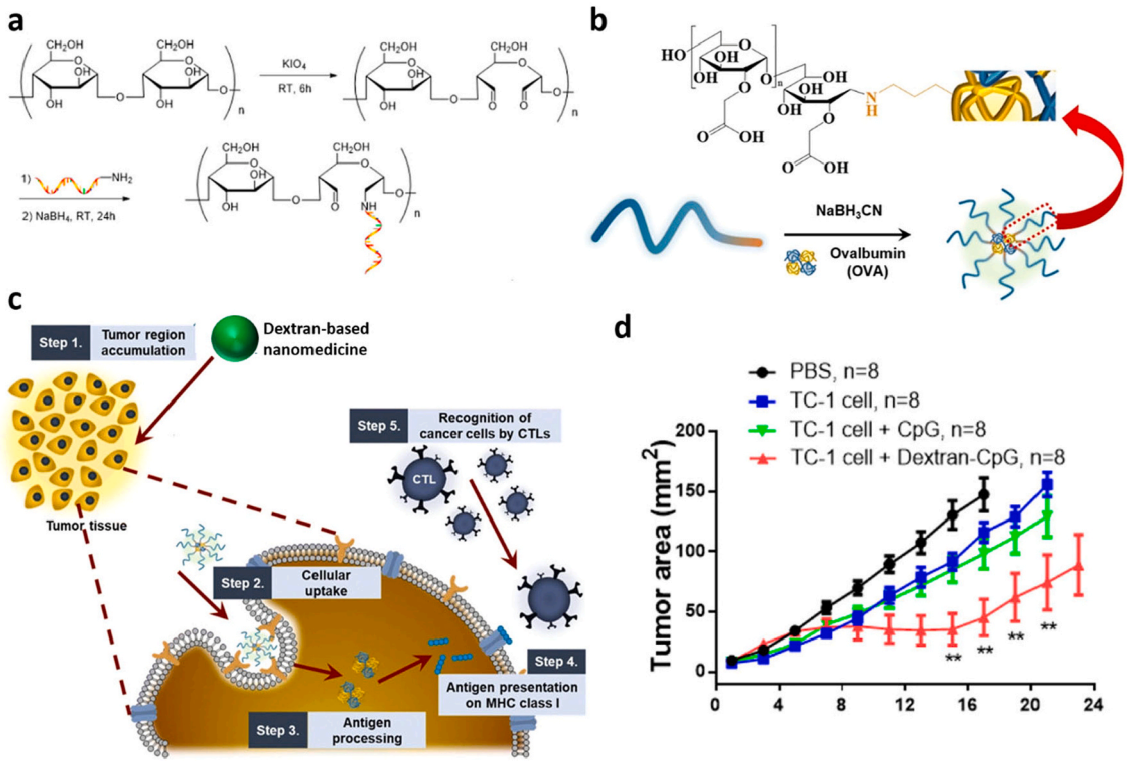


Fig. 7. Synthesis of type B CpG DNAs conjugated dextran-based nanoparticles (a) and carboxymethyl dextran-ovalbumin (b) and their therapeutic efficacy on cancer immunotherapy. Through improving the reorganization of tumor associated antigens by antigen presenting cells (c), these dextran-based nanomedicines could effectively enhance anti-tumor immunity thus resulting in the decreased tumor sizes (d). $^{**}p < 0.01$. Reproduced with permission from Refs. [288,290]. Copyright 2017 American Chemical Society and 2018 BMC Open Access, respectively.

6. Alginate-based nanomedicines

Alginate is a linear polysaccharide that serves as one of the main components of marine brown algae cell walls. Due to the chemical structure and physicochemical properties of alginate, it is biocompatible, biodegradable and bioadhesive to mucosal surfaces [295,296]. Furthermore, the structure of alginate is versatile for modifications, and this could allow the incorporation of specific targeting and functional moieties onto alginate to improve the mechanical strength, gelation, and cell affinity of alginate-based nanomedicines [297,298]. Thus alginate-based materials have been widely studied for their biomedical applications. Recent studies have utilized alginate to prepare functional nanomaterials and applied them to immune treatment of cancer diseases.

Since alginate has been widely reported to interact with macrophages to exhibit the immunomodulatory effect [299–301], many studies have first evaluated the feasibility of using alginate-based nanomaterials to achieve macrophages-targeting delivery. Since macrophages are one of the major types of antigen presenting cells, tumor-associated antigens were often used in this delivery process. Zhu et al. [302] loaded alginate nanoparticles with ovalbumin$_{323–339}$ peptide and evaluated their therapeutic efficacy against the B16-OVA cancer model in the mice. They found that these OVA peptide-loaded alginate nanomedicines could be uptaken effectively by macrophages and promote activation of macrophages to demonstrate their anti-tumor function. By activating tumor-associated macrophages, these nanomedicines could also increase the production of IL-8, IL-1β, G-CSF, TNF and IFN-γ, which are all cytokines inducing or presenting tumor cell killing effects. Another ε-polylysine-sodium alginate self-assembled nanoparticles have been applied to deliver exogenous antigens into macrophages [303]. These alginate-based nanosystems could effectively deliver antigens into macrophages and achieve sustained release of these antigens to boost the antigen presenting process and the down-stream adaptive immune response without any noticeable cytotoxicity.

In addition to targeting macrophage, alginate-based nanomedicines could interact with DCs. Zhang et al. [58] conjugated OVA to alginate-based aldehyde (ALG-CHO) through a pH-sensitive Schiff base bond and then assembled the conjugate with mannose (MAN) modified alginate (MAN-ALG) to form MAN-ALG/ALG = OVA nanoparticles (Fig. 8). These ovalbumin-conjugated nanomedicines were demonstrated to enhance uptake of these nanomedicines and promote the cytosolic release of these OVA antigens in DCs. They could induce maturation of DCs, proliferation and activation of cytotoxic $CD8^+$ T cells, and increase the production of anti-tumor cytokines. Bencherif et al. [304] synthesized alginate-derived cryogel sponge vaccines to encapsulate GM-CSF and CpG ODN and achieved a similar efficacy of DC stimulation and population increase. This efficacy of the alginate-derived cryogel vaccine to enhance cancer immunotherapy was also confirmed by a recent study [305]. However, due to the very few studies being published related to this type of polysaccharide-based nanomaterial, the clinical applicability of it for delivering other therapeutic agents to enhance the immunotherapy efficacy is to be confirmed and validated.

7. Other polysaccharide-based nanomedicines

Polysaccharides are a big family of sugar-based natural polymers with a large variety of members. Besides the aforementioned polysaccharides, other types of polysaccharide-based nanomaterials have been explored in cancer immunotherapy. Some examples are discussed below and more conformation and *in vivo* studies are expected.

Pullulan is a polysaccharide produced by the *Aureobasidium pullulans* fungus and popularized as a food and oral hygiene additive. It has long been recognized for its great water solubility, biocompatibility and biodegradability, and no obvious toxicity, immunogenicity or mutagenicity has been noted [306–308]. Due to these properties, it has been

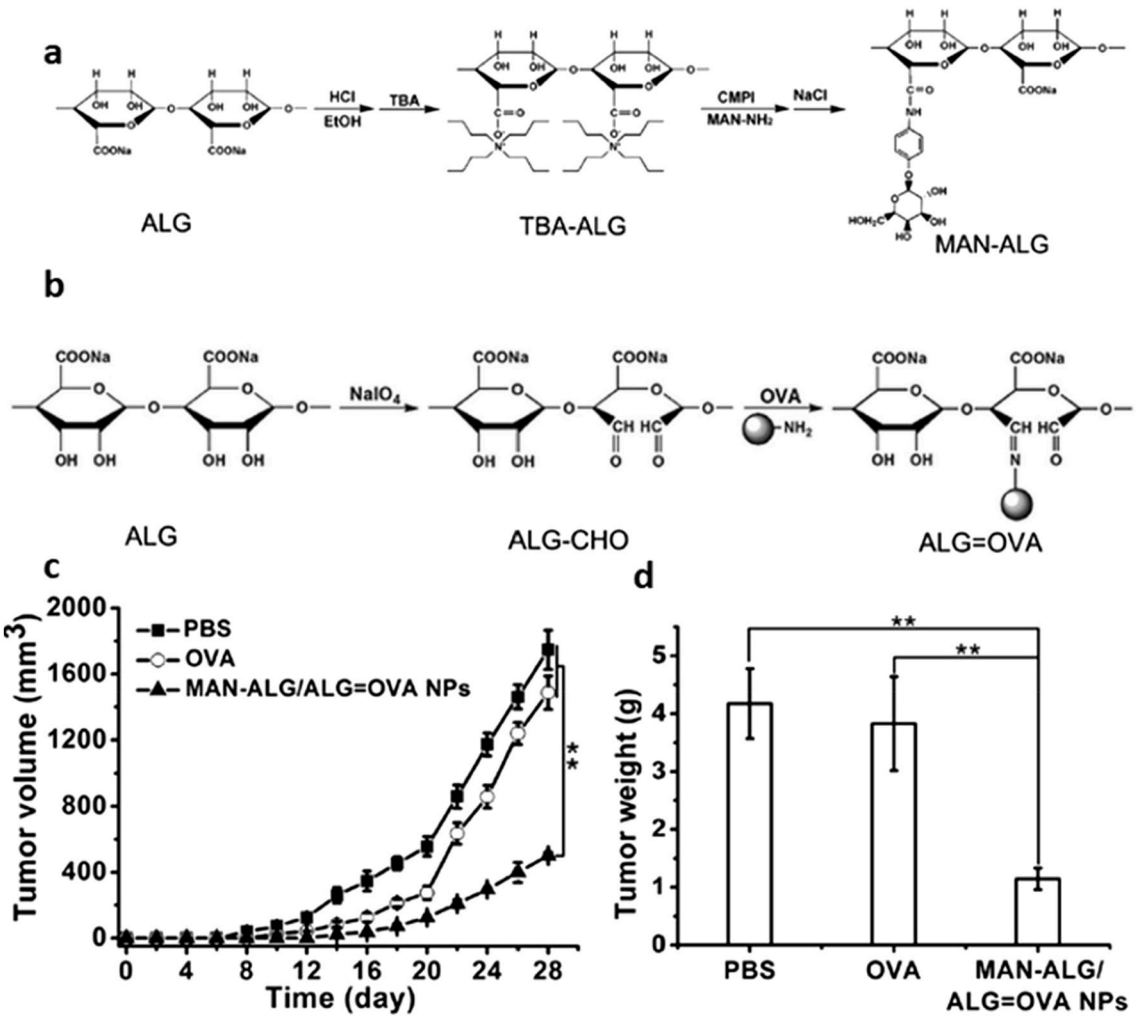


Fig. 8. Preparation of MAN-ALG (a) and ALG = OVA (b). ALG/ALG = OVA nanoparticles could significantly inhibit tumor cell proliferation by displaying a lower tumor volume (c) and a smaller tumor weight (d). $^{**}p < 0.01$. Reproduced with permission from Ref. [58], Copyright 2017 Elsevier.

explored in nano-scale drug delivery systems. Kyogoku et al. [309] discovered that cholesteryl-pullulan-melanoma antigen gene-A4 nanogels were effective in promoting tumor immune responses and they have entered a phase I + II clinical trial as a vaccine for cancer treatment. However, frequent administration of this vaccine may result in some undesirable changes in the anti-tumor immunity. Miura et al. [310] designed cholesterol-bearing pullulan (CHP) self-assembly nanogels to deliver OVA antigens. It has been discovered that this nanogel could selectively deliver OVA into the lymphatic system to be recognized by APCs. The anionic charge of the nanogel contributed to the enhanced interactivity of the loaded OVA with APCs, which induced strong adaptive immune responses towards tumor cells with enhanced activation of the Th1 immune pathway and the increased population of $CD8^+$ T cells. A previous study indicated that pullulan-based nanosystems could exhibit high affinity towards asialoglycoprotein receptors on hepatocytes [311], and they could be a promising targeting delivery platform for hepatocellular carcinoma. More studies on directly applying pullulan-based nanomedicines for hepatocellular carcinoma treatment are still demanded.

Chondroitin sulfate is another polysaccharide that could be used in the drug delivery system. It has been reported that modified chondroitin sulfate could exhibit low hydrophilicity to protect the loaded drugs since the structure of chondroitin sulfate is similar to that of HA [312–314]. Okubo et al. [315]developed chondroitin sulfate-based pH-responsive liposomes to deliver OVA antigens for tumor therapy. They found that these chondroitin sulfate derivative-modified liposomes could selectively deliver tumor-associated OVA antigens into DCs and increase the production of anti-tumor cytokines (Fig. 9). Their *in vivo* study also demonstrated a significant tumor growth inhibition effect of the OVA-chondroitin liposomes on growth and metastasis of tumors in the mice. Liu et al. also synthesized a chondroitin sulfate-based lipoic acid nanoplatform that was triple-responsive to redox, enzyme and ultrasound [59]. By conjugating Ce6 and loading docetaxel, this nanoconjugate could not only achieve a combinational therapy of sonodynamic therapy and chemotherapy, but also recruit cytotoxic lymphocytes into tumor tissues, resulting in an enhanced antitumor immune response. During the sonodynamic therapeutic process with this nanomedicine, ROS were generated in the tumor tissues. These ROS would activate innate and adaptive immune responses, promote the antigen release from tumor cells that DCs could recognize to induce and activate $CD8^+$ T cells [59].

β-cyclodextrin (CD), a low molecular-weight polysaccharide, has been also reported to be applied in the immunotherapeutic drug delivery [316,317]. It has seven glucopyranose units with a polar and hydrophilic external surface and a relatively nonpolar and hydrophobic internal surface, and this structure feature has been considered for delivery of immunotherapeutic agents. In a recent study, β-cyclodextrin was covalently reacted with lysine to form crosslinked CD nanoparticles (CDNPs) [60]. These nanoparticles were able to load R848 and deliver it to tumor tissues. These drug-loaded CDNPs could selectively target

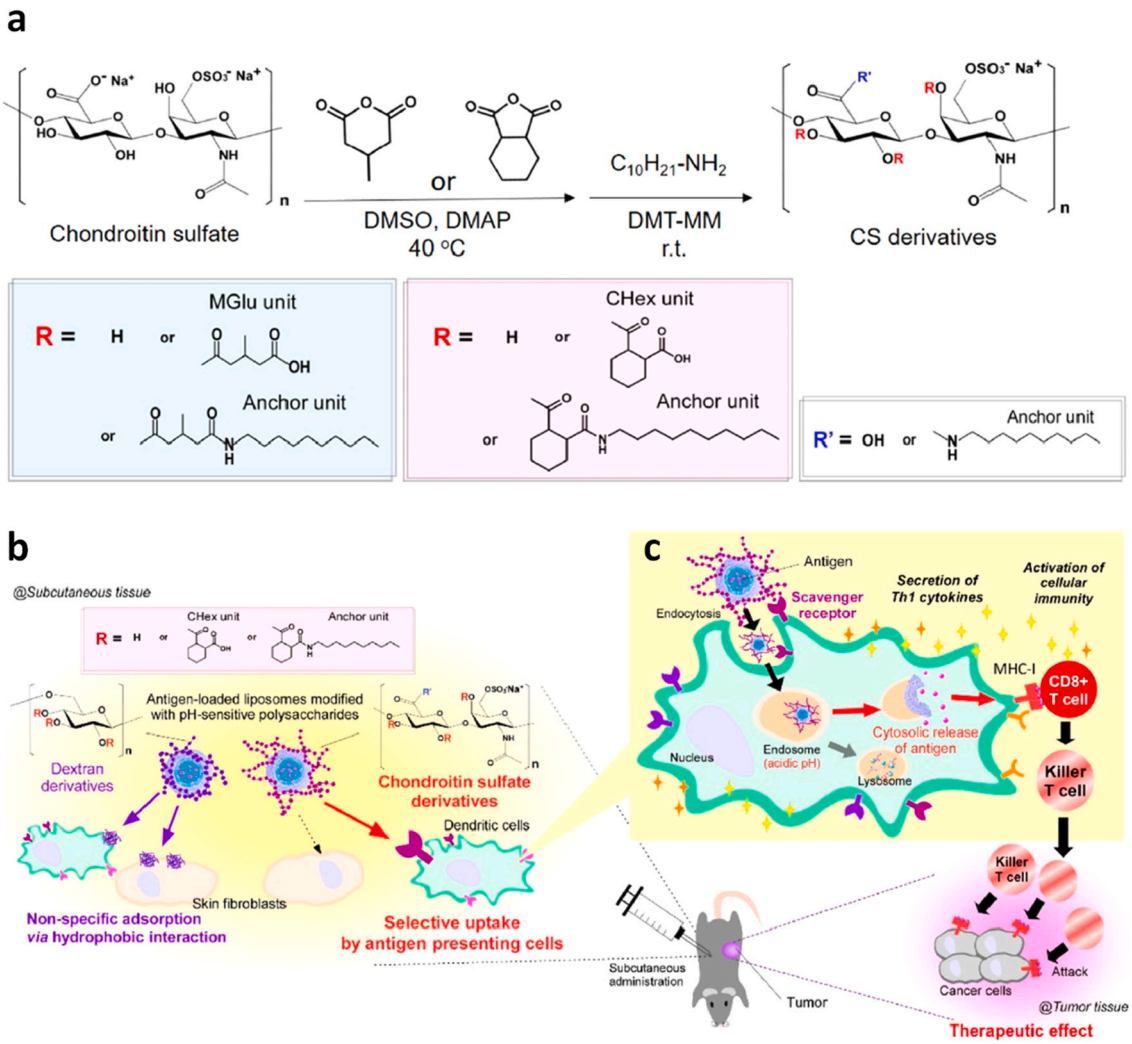


Fig. 9. Synthesis of chondroitin sulfate derivatives that could modify liposomes (a) and bioreaction of chondroitin sulfate derivatives-modified liposomes for stimulation of cancer immunity in subcutaneous tissue (b) and tumor tissue (c). Reproduced with permission from Ref. [315], Copyright 2019 American Chemical Society.

tumor-associated macrophages and induce alteration of macrophages from a pro-tumor M2 phenotype into an anti-tumor M1 phenotype, resulting in suppression of tumor growth and protection of animals against tumor recurrence. Furthermore, it has also been discovered that these R848 loaded-cyclodextrin nanomedicines along with anti-PD-1 agents could demonstrate synergistic effects to achieve an enhanced immunotherapeutic efficacy [60].

Pectin is a dietary component in plant-based foods such as fruits and vegetables. It serves as one main component of plant cell walls from where it can be extracted. Modified pectin materials are reported to possess excellent biological properties which have been applied in the treatment of cancer [318,319]. Hira et al. [320]synthesized pectin-guar gum-zinc oxide nanocomposites that could be used in cancer immunotherapy. In their study, these nanocomposites were shown to induce activation of tumor cell killing processes and improve the tumor cell killing capacities of peripheral blood lymphocytes. It increased the production of anti-tumor cytokines IFN-h, IL-2 and TNF-α which further led to the killing of tumor cells and inhibition of tumor growth. A deep understanding of pectin-based nanomaterials and their immunotherapy applications will pave the way for clinical trials.

Another polysaccharide heparin has a long history of uses in clinical practice [321–323]. Its anticoagulation, anti-platelet aggregation and anti-thrombus functions make them versatile for a variety of clinical conditions [324,325]. Recently, application of heparin in cancer immunotherapy has been studied. Xia et al. [326] utilized low-molecular-weight heparin to coat dendrimer-based core-shell nanocomposites to deliver CpG ODNs for cancer chemo-immunotherapy. According to their study, this nanomaterials-based combination therapy could effectively enhance the maturation of DCs and increase the population of cytotoxic $CD8^+$ T cells. The coating of low-molecular-weight heparin would prevent the epithelial-mesenchymal-like transition of tumor cells and suppress their inhibition effect by damaging the arrangement of their actin cytoskeletons, thus presenting as a promising candidate for chemo- and immunotherapy of cancer diseases. Another study applied a similar core-shell nanostructure with gambogic acid, heparin and CpG ODN to treat hepatocellular carcinoma [327]. It has been reported that these nanomedicines could effectively increase the population of cytotoxic T cells, induce differentiation of Th1 cells and promote Th1-based antitumor immune responses, which contribute to cancer immunotherapy.

With their excellent biocompatibility and targeting ability, inulin and their derivatives have also been studied as a nanoplatform to deliver therapeutic agents to target certain cells or tissues [328–330]. Although the application of inulin-based nanomaterials to cancer immunotherapy is still at a very early stage, inulin acetate-based polymers have been reported to deliver exogenous antigens into DCs effectively [331]. These OVA-loaded inulin acetate-based polymers could be selectively recognized by DCs through TLR4 and induce the maturation of these cells. *In*

vivo experiments demonstrated that these nanomedicines could significantly increase the titers of serum antibodies such as IgG1 and IgG2a and the amount of cytokines like IL-4 and IL-10 to present strong immune responses towards tumor cells. By managing these OVA-loaded inulin acetate polymers, inhibition of metastasis of melanoma cells to lungs has been witnessed in the experimented animals [331]. The targeting ability to DCs and biosafety of these inulin-based nanosystems make them safe and effective carriers to deliver immunotherapeutic agents.

Herbal extraction polysaccharide is another substance which has recently been applied in cancer immunotherapy (Fig. 10). Zhang et al. [64] used polysaccharide extracts from a natural herb (*Ganoderma lucidum)* and gold to form gold-*Ganoderma lucidum* polysaccharide (GLP-Au) nanoparticles. Through their *in vitro* experiments, these GLP-Au nanoparticles could effectively promote the maturation of DCs and increase the transcription of anti-tumor cytokines. These nanosystems also induced differentiation and activation of $CD4^+$ and $CD8^+$ T cells. *In vivo* studies revealed that GLP-Au nanoparticles could significantly suppress tumor growth and its pulmonary metastasis. A significant increase in the number of $CD4^+/CD44^+$ memory T cells towards tumor immunity has been also witnessed. These *Ganoderma lucidum* polysaccharide has also been used to conjugate bismuth sulfide (GLP-Bi) nanoparticles to achieve radiotherapeutic applications [65]. Through this conjugation, these nanoparticles could not only increase the sensitivity of radiotherapy, but also prominently promote activation and maturation of DCs and increase the population of $CD8^+$ T cells, which further led to increased secretion of pro-inflammatory cytokines to enhance antitumor immune responses. These GLP-Bi inhibited the tumor growth simultaneously and suppressed metastasis [65]. In a more recent study [332] galactoxyloglucan extracted from *Tamarindus indica* seeds was utilized to improve the stability and pH tolerance of copper nanoparticles. According to this study, these galactoxyloglucan-processed nanomedicines could significantly induce antitumor immune responses so as to reduce the tumor burden. Their excellent biodegradability, biocompatibility and immune stimulatory effect warrant further investigations of their applications in cancer immunotherapy. *Astragalus membranaceus* extracted polysaccharide is another herbal polysaccharide to be synthesized as nanomedicines for cancer immunotherapy [333]. These herbal nanomedicines induced the radiation-induced abscopal effect and promoted the systemic anti-tumor immunity. Anti-tumor immune memory has also been enhanced so that not only primary tumor growth has been inhibited, but growth of secondary tumor remote to primary lesions was also suppressed. These

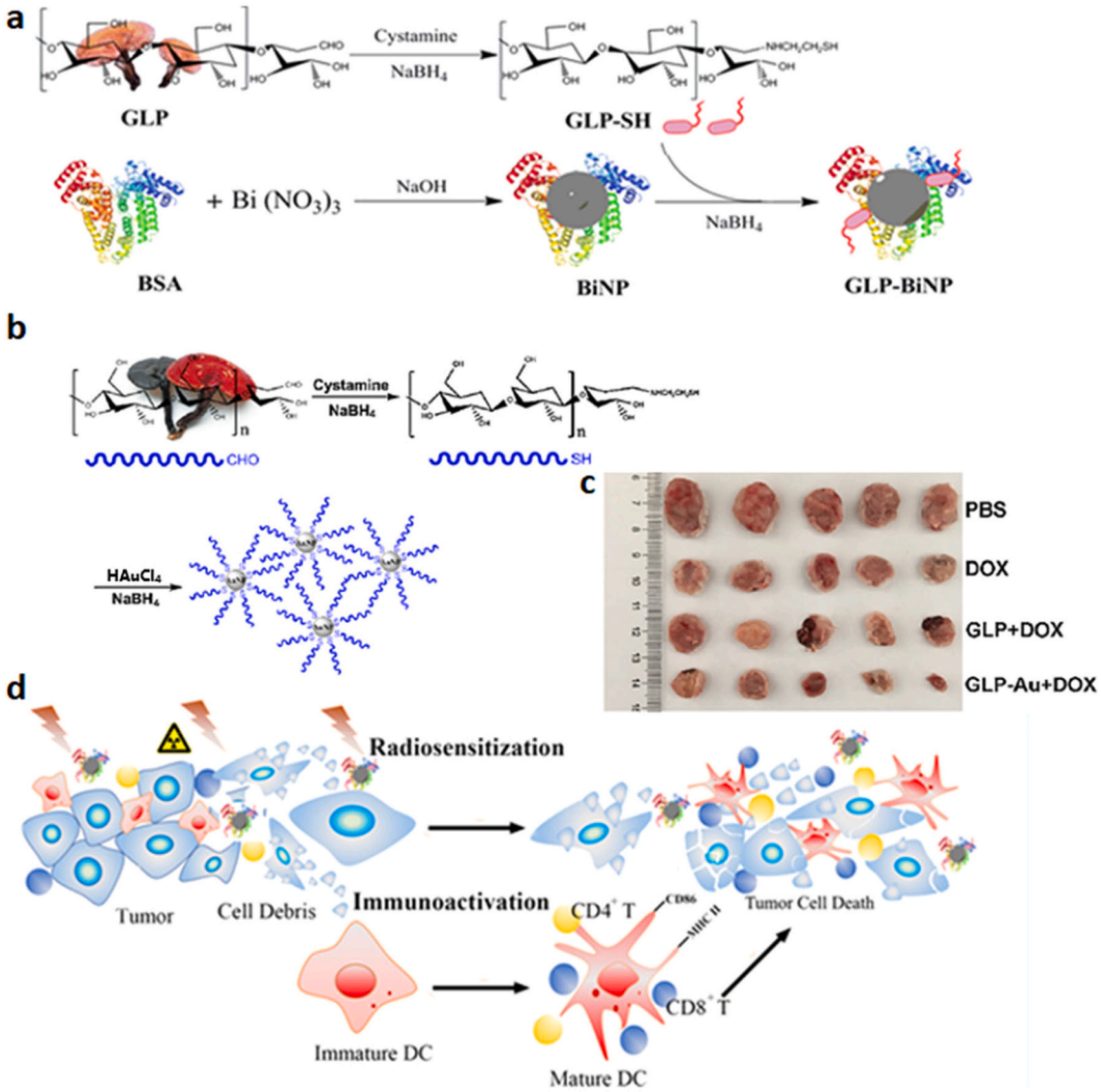


Fig. 10. Synthesis of GLP-Bi nanoparticles (a) and GLP-Au nanoparticles (b). GLP-based nanoparticles could effectively inhibit tumor growth (c) through the interaction with immune cells (d). Reproduced with permission from Refs. [64,65]. Copyright 2018 Elsevier and 2019 American Chemical Society, respectively.

natural herb-based nanomedicines may be feasible for both radiotherapy and immunotherapy against cancers. More recently, cationic polysaccharide derived from *Lepidium meyenii* Walpers has also been proven effective for tumor immunotherapy. This herb-extract nanomedicine could re-educate tumor associated macrophages to M1 phenotype, which alter the immunosuppressive tumor microenvironment into strong antitumor immune-activated, leading to the effective tumor growth inhibition [66]. Nevertheless, since many herbal extracts were reported to display short-term or long-term toxicities, whether these herbal polysaccharide-based nanomaterials would generate toxicities to normal tissues, especially in the long-term, is still in need of long-term assessments.

8. Conclusion and future perspectives

In summary, this review discussed recent progress of polysaccharide-based nanomaterials and their applications in cancer immunotherapy. These natural or modified nanomaterials, with their excellent physicochemical and biological properties, could be used as nano-carrier platforms to deliver immunotherapeutic agents such as adjuvants, cytokines, nucleic acids, and exogenous tumor-associated antigens. The polysaccharide nanomaterial-based drug delivery method could help to achieve targeting delivery of immunotherapeutic agents to immune cell subtypes and effectively improve the therapeutic efficacy of the loaded agents. Some of these polysaccharide-based nanomaterials could even play a role as an immunomodulatory agent in addition to enhancing the immunotherapeutic efficacy.

Despite these encouraging outcomes of polysaccharide-based nanomaterials for immunotherapy, a few key challenges of these polysaccharide-based nanomaterials need to be overcome, such as rational modification of polysaccharides, quantitative control of their molecular weight and the degree of modification, and incorporation of multi-stimuli-responsive moieties to achieve smart and programmable immunotherapeutic effects. Especially, some essential aspects of polysaccharide-based nanomaterials in immunotherapy are waiting to be investigated in future studies, including: 1) mechanistical studies of polysaccharide-based immunotherapeutics towards "precision" immunomedicines. For efficient immune cell-activation and tumor targeting, the mechanisms of polysaccharide-based nanoformulations and their immune-response properties need to be systematically elucidated, such as quantitative activation of immune cells (e.g. DCs, T cells, B cells and macrophages), intracellular localization of these nanoformulations and intercellular localization of these immune-substances, especially, related up/down-regulation of immune-responsive genes, proteins/enzymes; 2) Polysaccharide-based combinational cancer immunotherapy. Since tumorigenesis mechanisms differ individually, a single therapeutic agent may not be able to trigger enough immune responses to achieve satisfactory outcomes for cancer treatment. Therapy by combining multiple immunotherapeutic agents, namely combinational immunotherapy, is becoming an important strategy for tumor/cancer treatment. Some aforementioned studies have attempted to apply polysaccharide-based nanomaterials to deliver two different types of therapeutic agents for combinational therapy, but up to now, the number of related studies is very scarce. Moreover, how different immunotherapeutics are combined rationally, quantitatively, compatibly and synergistically into one nanosystem to achieve high-performance combinational immunotherapy remains a great challenge; 3) Clinical trials of the polysaccharide-based nanotheraputics from animal-models to human beings. Although several studies stated that their polysaccharide-based nanomaterials have demonstrated a satisfactory efficacy without obvious toxicities, there are still concerns on whether these nanomedicines could be administrated safely and effectively in the human body [334,335] since most of these experiments were conducted only in animal models while still in the absence of clinical trial data in the human body. A recent study has shown that naturally-derived HA had a wide range of molecular weights, ranging from a size of 10^4 kDa to be anti-angiogenic and immunosuppressive to 20 kDa to be angiogenic, immune-stimulatory and inflammatory. The immunotherapeutic effect of HA-based NPs with different molecular weights should be investigated in clinical trials [214]. Furthermore, clinical trials for cancer immunotherapy have their own unique considerations, and clinical trial designs should be tuned for these polysaccharide-based nanomedicines. For example, due to safety concerns of immunotherapeutics, the classical phase I 3 + 3 dose escalation may not be appropriate for continuous assessment of the relationship between their efficacy and toxicity. However, an adaptive and seamless phase I/II combined trial with multiple cohorts and continuous assessment of their efficacy and toxicity is recommended [336]. Furthermore, patient selection, clinical measurements, administration protocols, endpoint determination and analysis methods should be adjusted and harmonized in order to obtain safe, effective and regulatory body-acceptable clinical trial results [336–339]. The issues mentioned above may inspire future investigations/explorations on the development and improvement of polysaccharide-based nanomaterials, and these immunotherapeutic drug formulations would become mature for clinical cancer treatment.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgement

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Abbreviations

ACF	Acriflavine
APC	Antigen presenting cell
ATP	Adenosine triphosphate
Caco-2	Colorectal carcinoma
CAR-T cell	Chimeric antigen receptor T cell
Ce6	Chlorin e6
CMD	Carboxymethyl dextran
CpG ODN	Oligodeoxynucleotide
CPT	Cptothecin
CTL	Cytotoxic T lymphocyte
DC	Dendritic cell
DNase	Deoxyribonuclease
FDA	Food and Drug Administration
Fluc	Luciferase
GCS	Glycol-chitosan
GM-CSF	Granulocyte–macrophage colony-stimulating factor
HA	Hyaluronic acid
HLA-DR	Human leukocyte antigen-DR
HMGA	High mobility group protein A
ICOSL	Inducible co-stimulator ligand
IFN	Interferon
IL	Interleukin
LPH	Lipid-protamine-hyaluronic acid
LYVE	Lymphatic vessel endothelial
MAN	Mannose
MAPK	Mitogen-activated protein kinase
MATT	Marimastat
MMP	Matrix metalloproteinase

NF-κB	Nuclear factor kappa B
NIR	Near infrared ray
NK cell	Natural killer cell
NO	Nitric oxide
OVA	Ovalbumin
PAMP	Pathogen-associated molecule pattern
PANI	Polyaniline
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PEG	Polyethylene glycol
PEI	Polyethylenimine
PIGF	Placental growth factor
PLA	Polylactide
PLGA	Poly(lactic-*co*-glycolic acid)
PRR	Pattern recognition receptor
PTX	Paclitaxel
RHAMM	Receptor for HA-mediated motility
ROS	Reactive oxygen species
Th	T helper
TLR	Toll-like receptors
TNF	Tumor necrosis factor
TPP	Tripolyphosphate
Treg	Regulatory T cell
VEGF	Vascular endothelial growth factor
VES	Vitamin E succinate

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