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Drug delivery carriers with therapeutic functions

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ABSTRACT

Design of micro- or nanocarriers for drug delivery has primarily been focused on properties such as hydrophobicity, biodegradability, size, shape, surface charge, and toxicity, so that they can achieve optimal delivery with respect to drug loading, release kinetics, biodistribution, cellular uptake, and biocompatibility. Incorporation of stimulus-sensitive moieties into the carriers would lead to "smart" delivery systems. A further evolution would be to endow the carrier with a therapeutic function such that it no longer serves as a mere passive entity to release the drug at the target tissue but can be viewed as a therapeutic agent in itself. In this review, we will discuss recent and ongoing efforts over the past decade to design therapeutic drug carriers that confer a biological benefit, including ROS scavenging or generating, pro- or anti-inflammatory, and immuno-evasive properties, to enhance the overall therapeutic efficacy of the delivery systems.

Contents

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1. Introduction

The field of drug delivery has primarily been focused on carriers that can achieve properties such as high *in vivo* stability, delivery efficiency, and cellular uptake, all of which are dependent upon obtaining optimal size, surface charge, hydrophobicity, drug loading or encapsulation efficiency, and morphology, among other factors [1,2]. Optimizing the design of these parameters is crucial for achieving the desired delivery efficiency. However, there is still ample room to improve the carrier design by rendering the carrier itself therapeutic so as to enhance the overall therapeutic efficacy.

In this review, we will discuss recent and ongoing efforts over the past decade to design therapeutic drug carriers that themselves confer a medical benefit, such as immunomodulatory, anti-cancer, or anti-fibrotic properties to the patient and that can also enhance the effect of the loaded drug, without diminishing the effects of the drug alone. Importantly, this review aims to highlight materials which have inherent bioactivity without the aid of any additional pharmaceutically active ingredient, summarized in Table 1. This is a concept that has been studied over the past several decades, but research in this field has expanded rapidly within the past decade [3], thus we will focus on advances made during this time span.

Specifically, the major breakthroughs that have occurred in the field have been in reactive oxygen species (ROS) scavengers and promoters and danger-associated molecular pathway (DAMP)-targeting and immunomodulatory polymers to combat diseases such as cancer [4,5], fibrosis [6–8], autoimmune disease [9–11], and infectious diseases [12–14]. While there is overlap between these areas with respect to mechanisms of action, especially with

Table 1
Summary of notable examples and their mechanism of action.

Biological Function	Mechanism of Action	Notable Examples & References
ROS Scavenging	Cleavage of diselenide bonds in presence of oxidants	- SeNPs for cancer therapy [19] - SeNPs for RNase delivery [22]
	Catalyzing decomposition of H_2O_2	- MnO_2 NPs for anti-cancer therapy [24,25,27]
ROS Generating	Material acts as oxidant to induce ROS stress in low pH environment (i.e., TME), leading to apoptosis	- SeNP with 5-fluorouracil [28] - SeNPs for anti-cancer drug delivery [31,32] - CeO_2 NPs for anti-cancer drug delivery [34,35]
	Impair mitochondrial response and/or interrupt redox cycling	- AgNP for anti-cancer [37] or anti-bacterial [41] drug delivery - AuNP for cancer therapy [42,43] - Pluronic micelles for anti-cancer drug delivery [45,46]
Immuno-activating	Activation of cGAS-STING pathway, causing release of type I IFN and DC activation/ maturation, or cytotoxic T cell response	- CS NPs for vaccine delivery [66,67] - PC7A NPs for antigen delivery [99,100] - Synthetic LNP for mRNA delivery [101]
	Cytokine secretion and T cell proliferation	- LMW-HA-based microneedles for cancer vaccines [74,75]
	Activation of MyD88-dependent type I IFN secretion and NF-κB signaling pathways	- Pullulan nanogel for anticancer antigen delivery [81]
	B cell activation	- Alum NPs for immunogen delivery [86,87]
	Activation of macrophages with wound-healing phenotype	- PAMAM-G4 dendrimers for neural immune cell activation [98]
Anti-inflammatory	Binding of cell-free DNA (cfDNA)	- PAMAM-G3 for cancer [104] and autoimmune disease treatment [12]
	Chemoattraction of neutrophils	- CS scaffold for regenerative treatment [108,110]
	Inhibition of NF-κB and TNF-α pathways	- HMW-HA drug delivery systems for cancer treatment [116,117]
	Reduced cell adhesion	- Heparin nanosystems for wound healing [125,126]
Immuno-evasive	Modulation of lymphocyte and macrophage recruitment reduces myofibroblast recruitment and collagen deposition	- Alginate microcapsules for anti-fibrotic applications [134,137] - CS gel for glaucoma [140]
	Formation of protective hydration shells through electrostatic interactions lowers cell adhesion and reduced immune cell recruitment	- Poly-MPC coated alginate microcapsules for anti-fibrotic applications [129] - Sulfobetaine (SB)/carboxybetaine (CB)-coated microspheres for cell encapsulation [141]

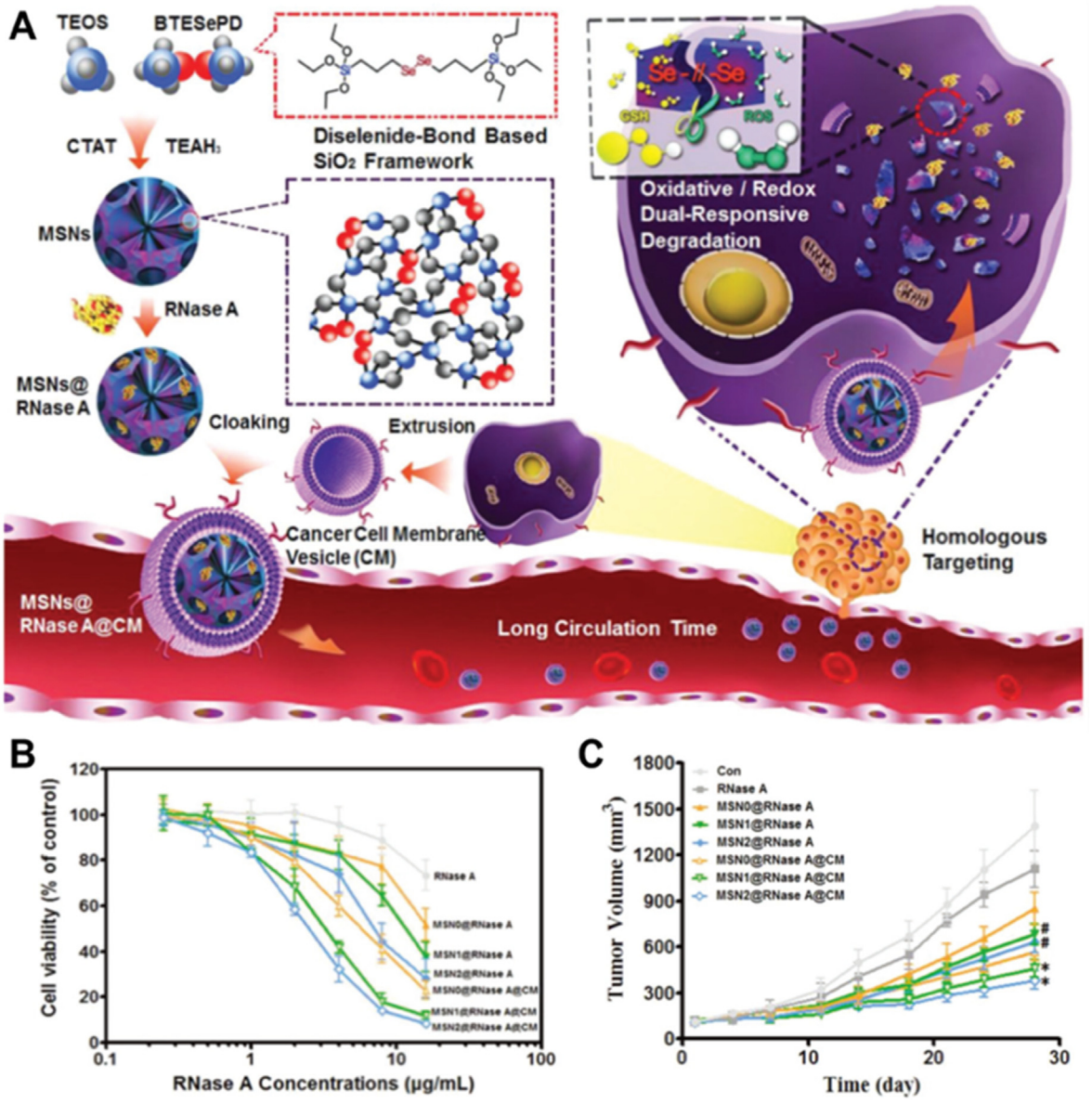

Fig. 1. Diselenide-bridged MSNs with ROS scavenging ability for redox-responsive release of RNase A. (A) Schematic illustration of biodegradable diselenide-bridged MSNs for protein delivery. (B) The cytotoxicity of MSNs against Hela cells at different concentrations for 48 h. MSN0 represents MSN with S-S bond (TEOS: BTESPT = 4:1), MSN1 represents MSN with Se-Se bond (TEOS: BTESePD = 4:1), and MSN2 represents MSN with Se-Se bond (TEOS: BTESePD = 3:2). (C) Tumor volumes of MSNs-treated HeLa-tumor bearing mice. Copyright 2018 WILEY-VCH. [22]

regard to modulation and regulation of immune pathways, we will focus on materials in two key areas that have gained momentum in the past decade: ROS-targeting and immunomodulatory carriers.

2. Carriers with ROS targeting activities

Reactive oxygen species (ROS) represent a series of chemically active oxygen-containing compounds, such as hydrogen peroxides, hydroxyl radicals, superoxides and so on. They are widely distributed in human bodies as natural byproducts of normal metabolism. Importantly, ROS at normal levels are essential to maintaining redox balance in human bodies, but high levels of ROS may induce cell apoptosis and cause ROS damage to normal tissues [15]. Thus, ROS play significant roles in human health, with meaningful implications in cancer treatment [4,5].

In the 21st century, cancer has long been ranked as the leading cause of death all over the world. In more than half of all countries throughout the world, cancer is the first or second cause of death among people younger than 70 years old [16]. Currently, chemotherapy based on hydrophobic small molecule drugs is still one of the most widely applied cancer treatments. However, these clinical chemotherapeutic drugs always face problems such as low solubility, fast elimination, and severe side effects. To solve these problems, drug delivery systems were developed to enhance solubility, stability, and tumor targeting efficiency. To further improve upon this traditional method, researchers have more recently begun investigating drug delivery vehicles that possess therapeutic effects on their own. Most efforts are focused on ROS-targeting activities, which can be combined with chemotherapeutic drugs to achieve higher anticancer activity and fewer side effects.

2.1. ROS scavenging

As previously mentioned, many cancer treatments can elevate ROS levels in both tumor tissues and healthy tissues. High ROS levels in tumor tissues are desired to kill cancer cells. However,

in healthy tissues, elevated ROS levels also induce cell apoptosis in normal cells, which cause severe side effects. Nanomaterials with ROS scavenging ability may protect the human body by scavenging the overproduced ROS. Additionally, the tumor microenvironment (TME) is known to possess high ROS levels; thus, nanomaterials with ROS scavenging ability may alleviate the oxidative stress in the TME and facilitate cancer treatments.

2.1.1. Selenium-containing nanomaterials

Selenium (Se) nanoparticles have been widely applied as drug carriers to encapsulate anticancer drugs such as cisplatin and doxorubicin (Dox) in recent years. Se-containing compounds are regarded as antioxidants because selenium acts as the active center of glutathione peroxidase (GPx), which has the ability to regulate redox balance [17,18]. Diselenide bonds can be cleaved in the presence of oxidants such as hydrogen peroxide and other types of ROS. The use of diselenide-containing nanomaterials for drug delivery was first reported in 2010.

Ma et al. synthesized a diselenide-containing polyurethane block copolymer (PEG-PUSeSe-PEG), an amphiphilic polymer that can self-assemble into micelles and load anticancer drugs [19]. Upon exposure to 0.01% H_2O_2, the polymeric micelles disassembled to release the loaded small molecule drug. The results indicated diselenide bonds in the polymeric micelles could react with H_2O_2 in physiological conditions, which revealed the ROS scavenging ability of Se-containing drug carriers.

The ROS scavenging ability of Se-containing nanomaterials were further clarified by Li et al [20]. They fabricated Se nanoparticles coated with 11-mercapto-1-undecanol (Se@MUN), which exhibited ROS scavenging activity. The Se@MUN was reported to scavenge the cisplatin-induced overproduction of intracellular ROS, thus alleviating renal injury caused by cisplatin. In addition to chemotherapy, Se-containing nanocarriers can also reduce the toxicity of radiotherapy. A γ-radiation-responsive diselenide-containing hydrogel was developed as a drug delivery system to load naproxen. Upon exposure to γ-radiation, diselenide bonds on the backbones of the hydrogel were cleaved, leading to the sol–gel transition and drug release. At the same time, diselenide bonds could scavenge γ-radiation-induced ROS, which may protect healthy tissues from radiation-induced injury [21].

Recently, multifunctional diselenide-bridged mesoporous silica nanoparticles (MSNs) were developed for delivery of RNase A (Fig. 1**A**) [22]. Diselenide-containing organo-silica moieties were incorporated into the silica framework to fabricate MSNs. RNase A was encapsulated into the internal pores via electrostatic interaction. The MSNs were further cloaked with cancer-cell-derived membrane fragments. The nanoparticles achieved controlled release of RNase A upon exposure to oxidative conditions and showed efficient *in vitro* and *in vivo* anticancer performance (Fig. 1**-B-C)**. Diselenide bonds also endowed the nanoparticles with ROS scavenging ability, which would reduce the side effects of common cancer therapeutics.

2.1.2. Manganese nanoparticles

ROS scavenging ability was also reported in manganese (Mn) nanoparticles. Based on the catalytic ability of manganese dioxide (MnO_2) to induce decomposition of H_2O_2, Prasad et al. hypothesized that manganese dioxide might exhibit peroxidase-like activity in physiological condition. They confirmed the hypothesis and fabricated bovine serum albumin (BSA)-stabilized MnO_2 nanoparticles with ROS scavenging ability. It is well known that elevated levels of ROS and insufficient oxygenation are abnormalities of the TME. Mn nanoparticles can scavenge ROS and produce oxygen at the same time, thus showing great potential for modulating the TME in cancer treatment [23].

According to this concept, manganese nanoparticles were combined with a photosensitizer to achieve enhanced photodynamic therapy (PDT), which involves the use of light to activate a photosensitizing agent to produce ROS to induce cell death. Chlorin e6 (Ce6) was loaded into polyethylene glycol (PEG)-modified Mn nanoparticles [24]. Mn nanoparticles scavenged the high levels of H_2O_2 within the TME to generate oxygen and carried Ce6 into tumor tissues. Ce6 consequently achieved tumor-specific PDT, which was promoted by the increased intracellular oxygen levels. The multifunctional nanoparticles exhibited remarkably improved antitumor efficacy in a mouse model compared with free Ce6. This highlights the significant roles encompassed by Mn nanoparticles, which act as both drug carriers and ROS scavengers.

Moreover, Fang et al. anchored Mn nanoparticles on the surface of hollow mesoporous silica nanoparticles (MSNs) to fabricate nanocarriers for Dox and Ce6 co-loading [25]. The nanoparticles triggered the decomposition of intracellular H_2O_2 and acted as a gatekeeper to control the release of Dox and Ce6. This multifunctional nanoparticle effectively suppressed cervical cancer, suggesting further applications of Mn-based nanosystems for cancer treatment. The synergistic therapeutic effect between chemotherapy and PDT can also trigger antitumor immune responses [26]. If further combined with checkpoint-blockade immunotherapy, the Mn-nanosystems would inhibit tumor growth at distant sites, which could be applied to treat tumor metastasis.

Photothermal therapy (PTT) is analogous to PDT, but uses heat activation as opposed to light, and can also be achieved in manganese nanosystems by encapsulating Prussian blue, a thermosensitive dye. Peng et al. designed Prussian blue/MnO_2 nanoparticles coated with red blood cell (RBC) membrane [27]. The Mn-based nanoparticles can load Dox, and upon exposure to high levels of H_2O_2 in the TME, the nanoparticles generated oxygen to attenuate the hypoxic environment. The generated oxygen disrupted the RBC membrane as well, which triggered the release of Dox and Prussian blue. Therefore, a combination of chemotherapy and PTT was achieved.

2.2. ROS generation

In contrast to ROS scavenging, ROS generation can induce cell apoptosis, which occurs when a high concentration of ROS is present in mitochondria. This mechanism can also be harnessed for cancer therapy. Tumor cells contain a higher concentration of innate ROS compared with normal cells, probably due to the improved glycolysis and pentose phosphate cycle. In this regard, tumor cells are normally more vulnerable to additional ROS generation. Therefore, many cancer treatments with the mechanism of ROS generation exhibit selectivity between cancer cells and normal cells, leading to minimal side effects. Nanomaterials with ROS-generating ability when used as a drug carrier may achieve a synergistic effect with other therapies, resulting in higher antitumor efficiency.

2.2.1. Selenium-containing nanomaterials

Although Se-containing compounds have long been known as antioxidants, their ROS-generating ability was gradually revealed over the past decade. The role of selenium-containing compounds varies between ROS scavenging and ROS generating, which depends on structure, concentration, and microenvironment. Selenium-containing compounds are commonly considered to cause extensive formation of ROS with increasing concentration of selenium [18]. Additionally, they tend to exhibit higher toxicity in cancer cells than in normal cells due to the high oxidative stress in cancer cells. This property indicates Se-containing compounds with ROS generating ability can show promising chemotherapeutic effects in cancer treatment.

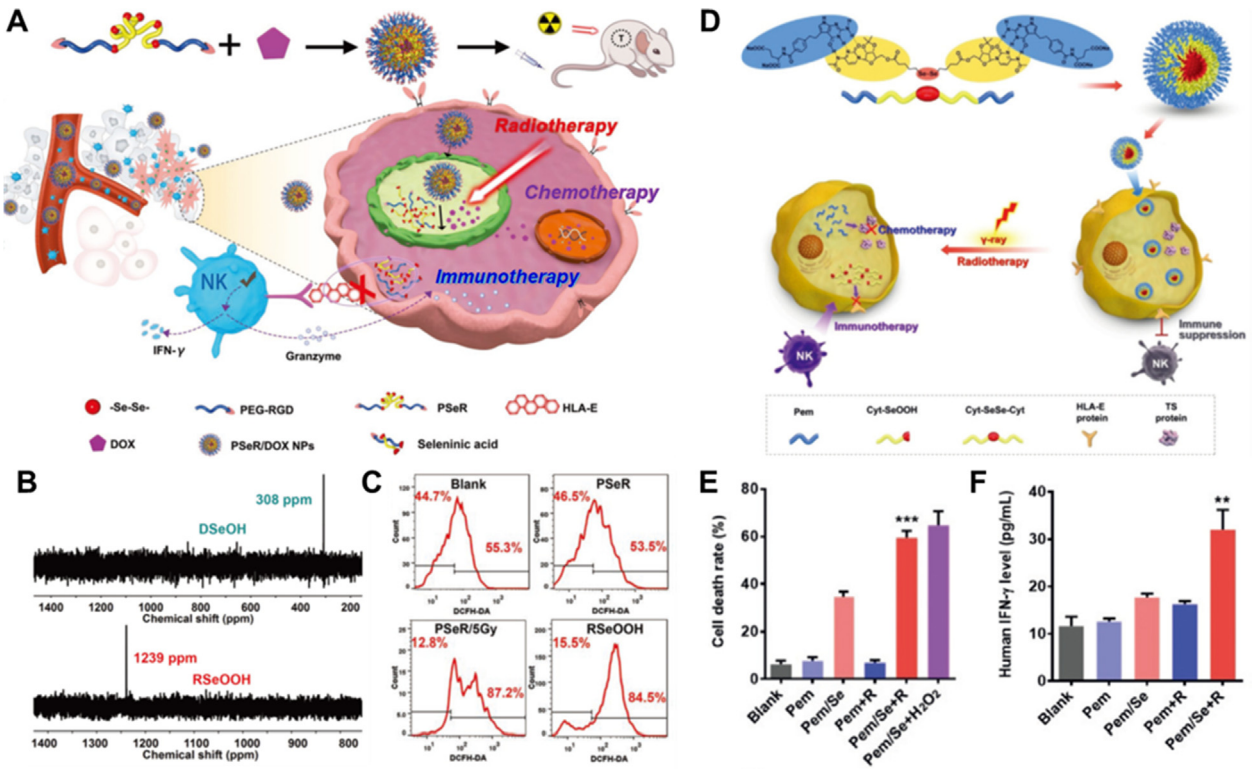

Fig. 2. Diselenide-containing nanoparticles combining treatment of chemotherapy, radiotherapy, and immunotherapy. (A) Schematic illustration of DOX loaded diselenide-containing polymers for combination therapy. (B) 77 Se-NMR spectra indicating the formation of seleninic acid under γ-radiation. (C) Flow cytometry spectra demonstrating the generation of ROS. (D) Schematic illustration of pemetrexed loaded diselenide-containing self-assembled NPs for combination therapy. (E) Lactate dehydrogenase assay indicating the cell death rates of MDA-MB-231 cells co-cultured with NK92 cells. (F) ELISA results exhibiting the IFN-γ levels produced by NK92 cells in co-culture system. Copyright 2020 WILEY-VCH. [31–32]

Liu et al. prepared selenium nanoparticles (SeNPs) with a simple method, which induced caspase-dependent apoptosis in cancer cells via ROS generation [28]. The selenium nanoparticles could load 5-fluorouracil by surface modification, which enhanced the cellular uptake of 5-fluorouracil and achieved anticancer synergism in an efficient way. They further developed Dox-loaded transferrin-conjugated SeNPs to confirm the antitumor activity of selenium-containing nanomaterials *in vivo* [29]. This study also demonstrated selenium-induced ROS overproduction, which activated p53 and MAPKs pathways to promote cancer cell apoptosis. Moreover, RGDfC peptide modified SeNPs were reported to co-deliver siRNA and Dox into HepG2 cancer cells, which exhibited high gene silencing efficiency and good chemotherapeutic effect [30]. Owing to the promising therapeutic effect, more SeNPs were developed recently as nanocarriers to treat cancer.

In addition, Gao et al. developed diselenide-containing nanomaterials with both ROS generating and drug loading ability (Fig. 2) [31]. The diselenide-containing amphiphilic polymers were prepared into nanoparticles with Dox loaded inside. Upon exposure to radiotherapy, the diselenide bonds were cleaved to form seleninic acid, which caused cell apoptosis by elevating intracellular ROS levels and activated anticancer immunity of natural killer (NK) cells. The cleavage of diselenide bonds triggered the disassembly of nanoparticles at the same time, and the encapsulated Dox was

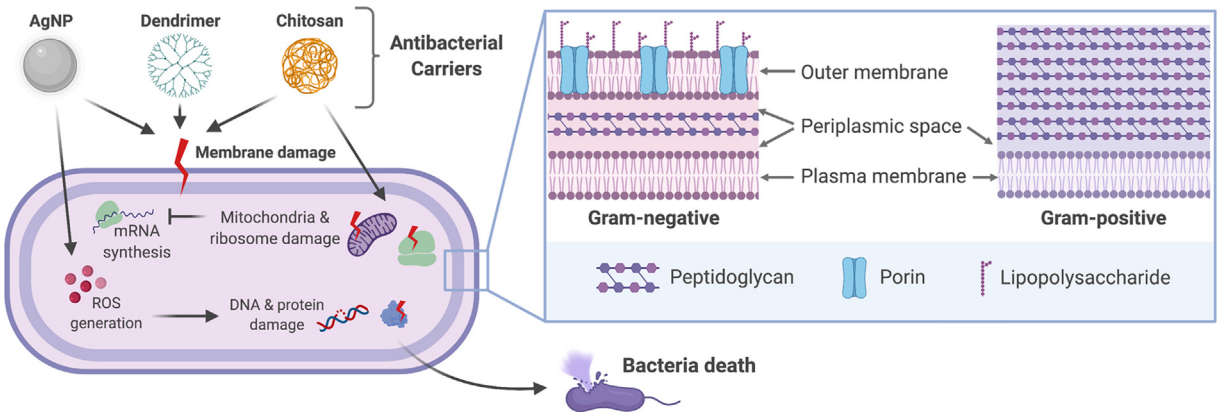

Fig. 3. Carrier interactions inducing anti-bacterial mechanisms. Inset shows differences between gram-positive and -negative bacterial membranes. (Adapted from [41], created with BioRender.)

consequently released. Thus, a combination of chemo-, radio-, and immuno-therapy was achieved by a simple and effective method (Fig. 2**A-C**). They also designed diselenide-containing self-assembled NPs loading pemetrexed through triple hydrogen bonds [32]. These self-assembled NPs simultaneously induced ROS production, improved anticancer immunity of NK cells, and released the chemotherapeutic drug pemetrexed (Fig. 2**D-F**). These studies suggest the potential of selenium-containing nanomaterials for cancer treatment.

2.2.2. Cerium oxide nanoparticles

Cerium oxide (CeO_2) nanoparticles are another type of nanomaterial that possess both ROS scavenging and ROS generating ability. In normal cells, they can act as antioxidant to protect cells from ROS damage. However, in cancer cells, they can act as an oxidant to generate ROS and induce apoptosis. CeO_2 nanoparticles play different roles at different pH values—in the low pH environment of cancer cells, CeO_2 nanoparticles are likely to induce ROS generation [33].

CeO_2 nanoparticles can act as drug carriers as well. Kalashnikova et al. fabricated CeO_2 nanoparticles coated with dextran and loaded with curcumin for neuroblastoma treatment [34]. The nanoparticles exhibited high toxicity to neuroblastoma cells with minor toxicity to normal neural cells owing to their unique selectivity. The nanoparticles induced prolonged oxidative stress, leading to caspase-dependent apoptosis in cancer cells. Combined with the chemotherapeutic effect of the controlled release of curcumin, the cerium-based nanosystem showed high efficiency in neuroblastoma treatment.

The aforementioned pH-responsive properties of CeO_2 nanoparticles can also be applied for controlled release of other chemotherapeutic drugs. Singh et al. developed MSNs capped with CeO_2 nanoparticles (COP@MSN) and loaded with Dox [35]. In the acidic environment of cancer cells, the capped CeO_2 nanoparticles degraded, resulting in the release of encapsulated Dox. The nanoparticles simultaneously induced high levels of ROS, achieving high anticancer efficiency via combination therapy.

2.2.3. Silver- and gold-based nanomaterials

Silver nanoparticles (AgNPs) have attracted much attention in the area of antiviral, antibacterial, and anti-inflammatory treatment. However, their applications in cancer treatment have not yet been thoroughly reviewed. Several studies have suggested that AgNPs can induce ROS generation specific to the acidic environment of tumor cells, and not in normal cells. This is hypothesized to be caused by impairment of the mitochondrial respiratory cycle and redox cycling via the Fenton-like reaction by released metal ions [36]. To this end, Li et al. fabricated polyethylenimine (PEI)-modified AgNPs loaded with paclitaxel. The nanoparticles elevated ROS levels and induced apoptosis in HepG2 cells [37]. AgNPs can also be stabilized by poly(amidoamine) (PAMAM) dendrimers, which encapsulated 5-fluorouracil to attain synergistic antiproliferative therapeutic effects in A549 and MCF-7 cells by inducing cell apoptosis, demonstrating the dual functions of AgNPs [38].

Additionally, owing to the oxidative stress caused by generation of ROS species, AgNPs can also lead to bactericidal activity. AgNPs have long been studied as antibacterial carriers due to their ability to damage the bacterial membrane structure and inhibit membrane enzymatic activity [13,39]. This is hypothesized to be due to the interactions between Ag + ions and sulfur groups in bacterial membrane proteins, thus attacking the respiratory chain and cellular division. Bacteria can lead to a variety of infectious diseases, including meningitis and tuberculosis [40]. The key mechanisms to inducing bactericidal activity, shown in Fig. 3, involve inhibition of any activities during the replication cycle, including DNA replication, protein synthesis, transcription, cell division, chaperone-assisted protein folding, etc., as well as inducing ribosome proteolysis or membrane alteration with cationic antimicrobial polymers (AMPs) [13]. These can be induced through a variety of methods, such as ROS generation for oxidative stress induction, and nitric oxide (NO) release. Of note, these anti-bacterial mechanisms differ slightly for gram-negative and -positive bacteria due to the differences in membrane structure, as gram-negative bacteria have an outer membrane composed of porins and lipopolysaccharides and thus are more difficult to attack (Fig. 3 **inset**).

To this end, Vazquez-Muñoz et al. investigated the synergistic effects of several conventional antibiotics when combined with AgNPs, which serve as both an antibacterial agent and a delivery vehicle, in various strains of gram-positive and -negative bacteria. Kanamycin and chloramphenicol exhibited an additive effect at a fractional inhibitory concentration index (FICI) of < 0.5 and 0.5–1, respectively. Conversely, β-lactam antibiotics showed no effect [41]. These results indicate there is potential for synergistic effects between AgNPs and antibiotic drugs, allowing for more efficient treatment of MDR bacterial infections.

Gold-based nanomaterials are also widely used in various applications of biomedical engineering. Their ability to generate ROS was likewise explored and applied to developing drug delivery systems with improved therapeutic effects. Gold nanoparticles (AuNPs) are well-studied as drug carriers for loading different types of anticancer drugs. Although they are typically considered to be biocompatible, Wang et al. revealed that gold nanorods could selectively accumulate in the mitochondria of cancer cells and increase ROS levels, leading to cell apoptosis [42]. The mechanism was explained by distinct pathways of cellular trafficking in cancer cells and normal cells. These mitochondria-targeting gold nanorods are thus ideal carriers for anticancer drugs specifically affecting mitochondria.

In addition, Zhang et al. fabricated peptide template gold clusters that catalyzed the transformation of H_2O_2 into superoxide anion in cancer cells [43]. Since superoxide anion is a type of ROS that causes more damage than H_2O_2, the formation of superoxide anions caused by the gold clusters induced elevation of ROS levels in cancer cells, thus triggering cell apoptosis. AuNPs can also be applied to many other cancer treatment modalities, such as in combination with photodynamic therapy (PDT), to treat cancer cells via ROS generation.

2.2.4. Pluronic micelles

Finally, pluronic micelles have been shown to reverse multidrug resistance (MDR) cancers, which are difficult to treat with traditional chemotherapies. Pluronics or poloxamers are a class of triblock copolymers consisting of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO), in the form PEO-*b*-PPO-*b*-PEO). They are currently used in clinical applications due to their known ability to inhibit the drug efflux transporter, P-glycoprotein (P-gp). Notably, they have been found to promote generation of ROS species, in addition to causing inhibition of respiratory chain complexes in the mitochondria of MDR cells [44,45].

In 2010, Batrakova et al. showed that a formulation of Pluronic 85 (P85) and doxorubicin (Dox), termed Dox/P85, successfully inhibited tumor growth through promotion of apoptosis, as well as tumor accumulation of P-gp substrate and ATP depletion in animal models of lung carcinoma- and leukemia-derived MDR solid tumors [45]. Specifically, tumor cell apoptosis was evidenced by high relative fluorescence in tumors treated with Dox/P85 stained by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay and up to six-fold upregulation of caspase 8 and 9 (pro-apoptotic genes). A similar study by Chen et al. demonstrated the ROS-generating ability of Pluronic 105 (P105) and F127 delivering methotrexate (MTX) [46].

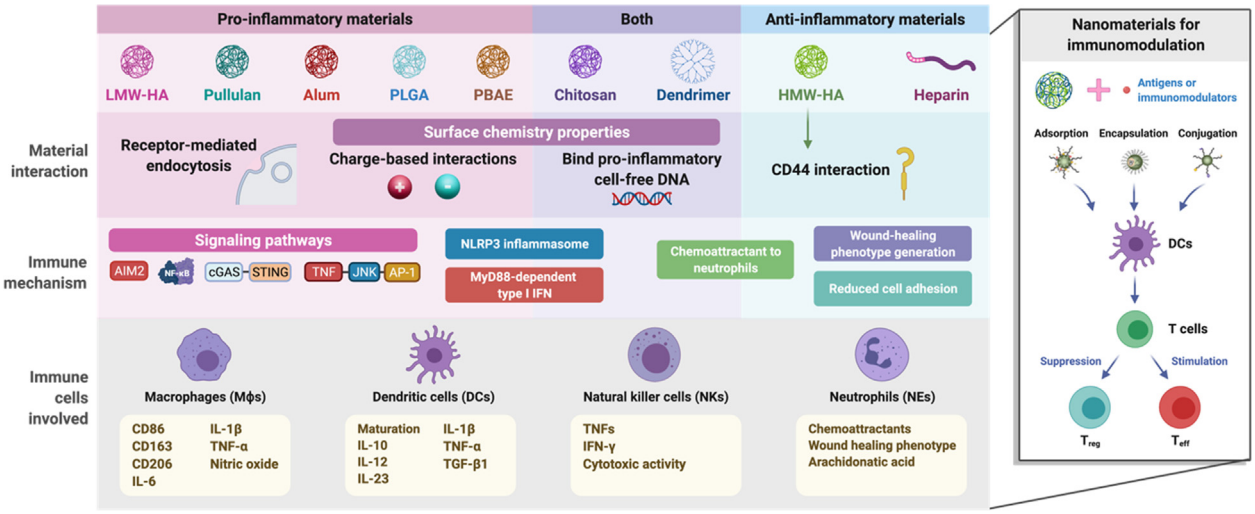

Fig. 4. Materials interactions and immunomodulatory effects of carriers targeting DAMP-associated pathways. Inset on right shows general mechanisms employed by nanomaterials for immunomodulation. (Created with BioRender.)

2.2.5. Biosafety of ROS generating carriers

Biosafety is one of the major barriers that limits the clinical application of drug delivery carriers. Some nanocarriers, especially those based on metals, were reported to induce DNA damage or oxidative damage in normal tissues. The potential toxicity of ROS generation carriers mainly focus on the overproduction of ROS in normal tissues, which may induce inflammation when accumulated in organs, such as liver and kidney [47].

Different strategies were developed to enhance the biosafety of drug delivery carriers. Improving the targeting efficiency of carriers is one of the choices [48]. Carriers that specifically target tumor tissues or release drugs in specific tumor environment were constructed to reduce the biodistribution of drugs in normal tissues, thereby reducing the potential toxicity. Developing carriers with selective toxicity to cancer cells and normal cells is another strategy. Based on the fact that most cancer cells are more vulnerable to additional ROS generation, many ROS generation carriers were reported to exhibit higher toxicity to cancer cells than that to normal cells. Further modifications can be performed to reduce the immune response and accelerate the elimination process. For example, the surface of drug delivery carriers can be modified with biocompatible polymers; the core of carriers can be modified with cleavable linkages to improve biodegradability. Carriers with good biosafety are always desired for clinical applications.

3. Carriers with DAMP-targeted activities

Autoimmune diseases are responsible for the progression of tissue destruction or dysfunction and are caused by antigenically complex immune responses against specific cells, tissues, or host organs [49]. Immunoregulation therapy offers a number of potential methods to amplify or rewire the immune system. However, antigen-specific therapeutic methods using antigenic peptides or proteins to induce immune tolerance in autoimmunity have failed to procure the coveted therapeutic outcome in clinical testing [3]. Immunomodulatory drug delivery systems can readily improve therapeutic outcomes while surmounting many of the obstacles to therapeutic approaches, including insufficient immune stimulation, off-target effects, and loss of biological activity of immune agents [50]. Specifically, pro-inflammatory materials can elicit the release of pro-inflammatory cytokines and induce enhanced immune responses and resistance to bacterial infections, while anti-inflammatory materials can inhibit the release of inflammatory mediators or mitigate the dysregulation of pro-inflammatory cytokines along with increasing the release of anti-inflammatory cytokines, thus minimizing the host response [51].

Recently, many works have probed into the design and modification of both natural and synthetic materials for promoting immune tolerance through various mechanisms, ranging from systemic inhibition of antigen presenting cells (APCs) and deletion of antigen-specific T-cells, to the systemic expansion of disease-specific regulatory T-cells *in vivo* [52]. In this section, we will constrain our focus to the development of natural and synthetic nanocarriers for the treatment of autoimmune disease and inflammatory conditions. First, we will shed light on the natural polymers which may shape the immune system for prophylactic or therapeutic purposes and provide a more effective alternative to cancer treatment. Fig. 4 summarizes the mechanisms of immune regulation of these immunomodulatory materials.

Most natural nanomaterials illustrated in this section share the important benefit of biocompatibility and biodegradability in addition to immunoregulatory effects. Polysaccharide nanoparticles, along with alum nanoparticles, show enormous potential to serve as nanomedicines toward immune system diseases and anticancer therapy. With the progress in the development of such polymer systems for immune disorders, their distinct properties have permitted clinicians to harness them either as novel treatments (monotherapy) or as adjuvants to existing treatments (combination therapy) to enhance therapeutic efficacy [53].

3.1. Immunoactivation

The intrinsic immunomodulatory effects of biomaterials can be harnessed to ameliorate human conditions either via immunostimulatory or immuno-suppressive effects. This is a unique area as immuno-inert, natural biomaterials have been studied for decades [10]. These advanced materials can be applied to the treatment of cancer, autoimmune diseases, and infectious diseases [9]. The Wyss Institute for Biologically Inspired Engineering at Harvard University recently established their "Immuno-Materials" focus area that centers on harnessing immunomodulatory materials, such as a biomaterial scaffold to attract and trap disease-related T-cells, to make treatments more effective [54].

Over the last decade, investigators have begun to determine the specific effects that biomaterials can have on players in the immune system. This includes immune cell types such as antigen

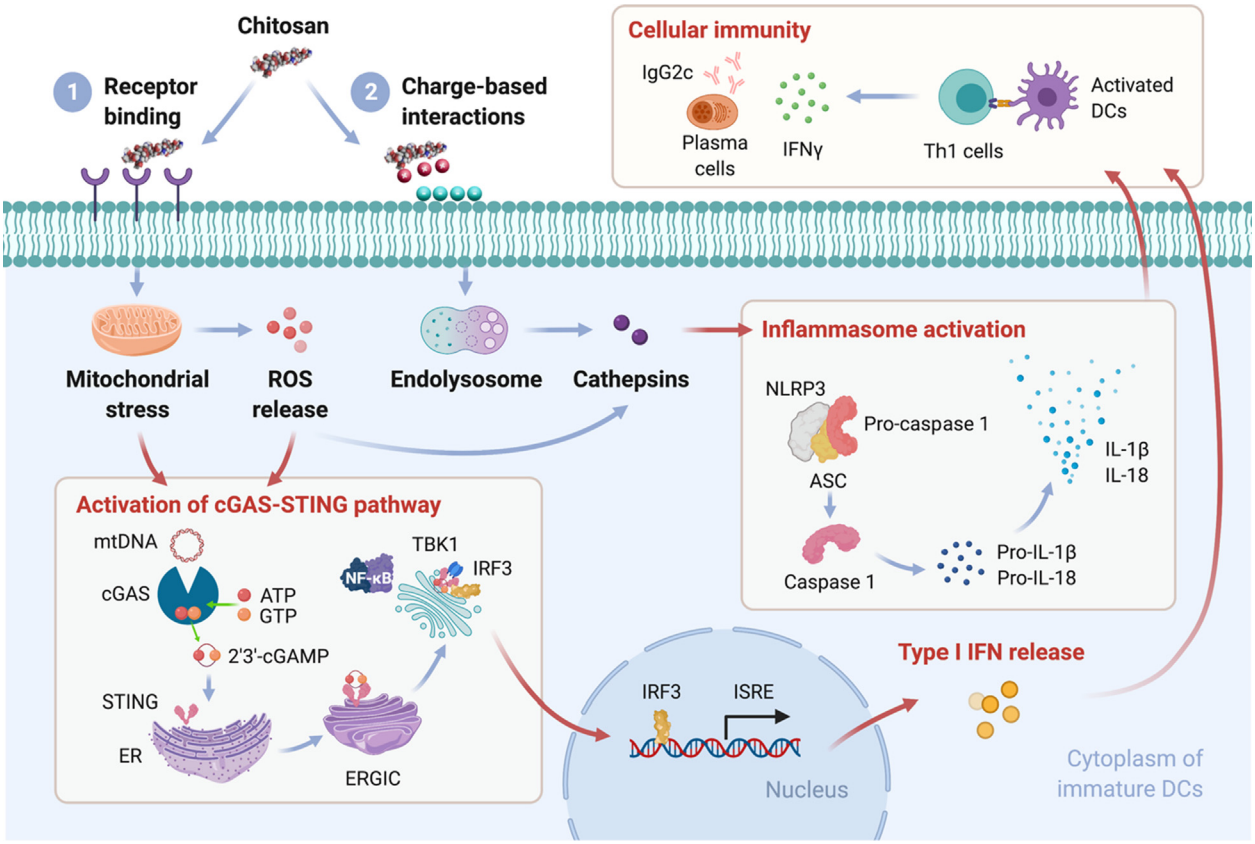

Fig. 5. Chitosan-mediated cGAS-STING and inflammasome activation, and the promotion of Th1 responses. Chitosan receptor binding and charged-based interactions with host cell triggers the cGAS-STING pathway and the NLRP3 inflammasome. cGAS-STING pathway induced by CS may further lead to the activation of IRF3 and NF-κB, inducing the transcription of genes encoding type I IFNs and proinflammatory cytokines. (Created with BioRender.)

presenting cells (APCs), T cells, B cells, and natural killer (NK) cells [9]. A diverse portfolio of both natural and synthetic nanocarriers have been discovered with intrinsic pro-inflammatory properties, and these materials have been utilized to mediate targeted delivery of various antigens and adjuvants or immune regulatory agents in ways unachievable with conventional drug or vaccination approaches.

3.1.1. Chitosan for inflammatory activation

Chitosan (CS) is a mucoadhesive cationic polysaccharide, comprising a large class of biopolymers ranging in their deacetylation (40–98%) and molecular weight (M_W = 50–2000 kDa) [55]. As part of the polysaccharide family, the main characteristics of CS are biocompatibility, biodegradability, antibacterial properties, non-toxic safety profile, and low immunogenicity, all of which endow it potential in biomedical applications such as wound dressings and adjuvants in human vaccines and bolster the transmucosal absorption of peptides and proteins [56].

CS has also been known to engender both pro-inflammatory and anti-inflammatory effects. Early research demonstrated that CS has considerable immunomodulatory ability to activate macrophages and induce cytokine secretion from natural killer (NK) cells [57]. The exposure of primary human monocytes to CS may lead to the major differentiation toward M2 phenotype macrophages, as indicated by the down-regulation of CD86 and MHC II along with the up-regulation of CD206 [58]. These interactions have been shown to occur in a phagocytosis-dependent manner to activate the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, inducing a robust IL-1β response [59]. The release of IL-1β can not only reinforce the priming of naïve T cells but can also boost the expansion of Th1, Th2 and Th17 cells [60]. Remarkably, Carroll et al. unveiled a new mechanism of CS action, including type I interferon (IFN)-dependent activation of dendritic cells (DCs) and intensification of antigen-specific T-helper 1 (Th1) responses, yielding enhanced DC maturation [61]. Specifically, CS could induce IFN-stimulated genes, type I IFNs, as well as DC maturation with the aid of the cyclic GMP-AMP synthase-stimulator of interferon genes (STING) pathway, which is implicated in DC activation.

Moreover, CS can provoke mitochondrial stress through receptor binding, which may lead to the generation of mitochondrial ROS and DNA release. After vaccination, the enhancement of CS-mediated antigen-specific Th1 and immunoglobulin G2c responses hinges on cGAS and the adaptor protein STING. The STING signaling pathway is essential for protecting the cell against various pathogens and even against the progression of cancer by boosting antitumor immune responses [62]. It is endogenously activated by cGAMP, a cyclic dinucleotide, synthesized by cGAS in response to cytosolic DNA as a danger signal [63]. Once exposed to double-stranded DNA (dsDNA), the cGAS-STING pathway can be activated, whereby cGAS binds to host nucleic acids, resulting in the production of cyclic dinucleotides which in turn bind to STING in the endoplasmic reticulum [64]. STING can form a complex with TANK-binding kinase 1 (TBK1), thus trafficking to the perinuclear Golgi through pre-autophagosomal-like structures, which eventually activates transcription factors NF-κB and IRF-3 [62]. CS can thus engage the latter downstream pathway of STING signaling to trigger innate and adaptive immune responses (Fig. 5). Consequently, the antitumor mechanisms of CS may also be enhanced by adaptive immunity to accelerate T-cell differentiation, thereby increasing cytotoxicity and maintaining T-cell activity, rendering it a useful material for antitumor treatment [65].

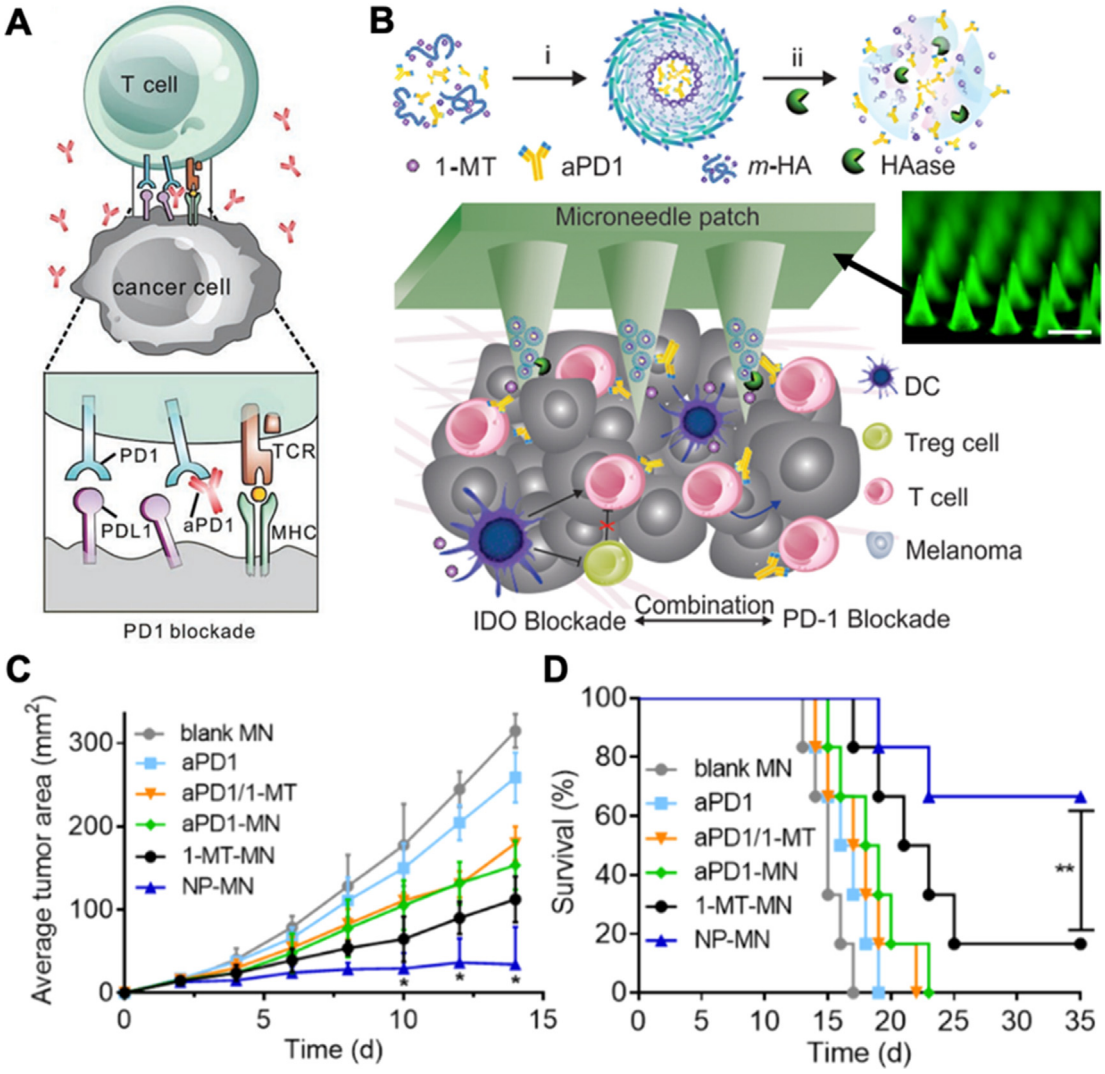

Fig. 6. Dissolvable microneedle array for sustained release of the checkpoint inhibitor. (A) Schematic illustration of encapsulation and release of IDO inhibitor 1-MT and aPD1. (B) The blockade of PD-1 via aPD1 may incite the immune system to demolish cancer cells in the skin. (C) Average tumor areas for the treated mice. (D) Survival curves for the treated and control groups. Reproduced with permission. [74–75] Copyright 2016, American Chemical Society.

For this reason, several studies have begun to investigate the use of chitosan for influenza nanovaccines. One such example is mucoadhesive chitosan nanoparticles (CS NPs) for delivery of swine influenza A virus (SwIAV) vaccine in pigs. After fabrication and delivery of chitosan SwIAV nanovaccine, Dhakal et al. observed an increased frequency of T-helper memory cells and unregulated levels of recall IFNγ secretion from tracheobronchial lymph nodes cells [66]. Enhanced antitumor immunity has also been achieved by targeting DCs with cancer cell lysate-loaded CS NPs vaccine.

Shi et al. revealed that CS can also enhance immunogenicity during vaccination, and CS NPs can be utilized to generate tumor vaccines, enabling controlled release of antigens in the desired manner [67]. In this work, CS NPs with surface decorated mannose (Man-CTS NPs) were fabricated and loaded with tumor cell lysates to target DCs specifically. This nanodrug delivery system can facilitate the maturation of bone marrow-derived dendritic cells (BMDCs) and presentation of antigen *in vitro*, yielding therapeutic effects in animal models of melanoma.

3.1.2. Low molecular weight hyaluronic acid (LMW-HA)

Hyaluronic acid (HA), a linear glycosaminoglycan formed via repeating units of N-acetyl-D-glucosamine and D-glucuronic acid with the monosaccharides, has been demonstrated to possess the immunoregulatory property to induce a specific and lasting immune response *in vivo* [53]. By altering the molecular weight, HA treatment may bring about disparate responses in the body.

Low molecular weight (≤300 kDa) HA (LMW-HA) acts as an inflammatory mediator and may trigger the stimulation of cell proliferation by receptor-mediated signaling pathways, whereas high molecular weight (>1000 kDa) HA (HMW-HA) can regulate the excessive inflammation, mainly owing to its inherent immunosuppressive effect [68]. Some studies suggest that the signal transduction performed by HA relies on its ability to aggregate receptors on the cell membrane. For example, HMW-HA has multivalent sites for CD44 binding, compared to 1 or 2 binding sites for LMW-HA [69]. Small HA fragments can incite an increase in cytokine production (i.e., IL-1β, IL-12 and TNF-α) and induce DC maturation [70]. The fragmentation of HA can lead to the ability of HA to influence certain receptors on cellular membranes. Another study found that LMW-HA could induce DC activation, cytokine secretion, and T cell proliferation, while HMW-HA did not [71].

To take advantage of the promising immunoregulatory effect of LMW-HA, Miyazaki et al. developed a pH-responsive LMW-HA-based antigen carrier to elicit antigen-specific cellular immune

responses. Recognized by CD44-expressing APCs, the obtained polymers exhibited a much higher cellular association to APCs than to fibroblasts, which have lower levels of CD44 expression [72]. In another study, biodegradable LMW-HA (27 kDa) modified with L-octaarginine was fabricated as a mucosal adjuvant with cross-protective abilities. Intranasal IgA with cross-reactivity was induced via nasal inoculation with inactivated whole viral particles of the H1N1 A/New Caledonia/20/99 IVR116 (NCL) strain in the presence of such biopolymer. The outcomes indicated that HA modification to generate a mucosal adjuvant could promote hosts to acquire adaptive immunity against heterologous virus infection [73].

Aside from applications in immunoregulation treatment as nanocarriers, HA has also shown great potential for use in transdermal microneedles. In 2016, Wang et al. reported a self-degradable microneedle patch composed of LMW-HA (300 kDa) integrated with dextran NPs for the sustained delivery of anti-PD-1 in a physiologically controllable manner **(**Fig. 6**A)** [74]. The controlled release profile was obtained by engulfing glucose oxidase to convert the blood glucose to gluconic acid and improve degradation of dextran along with anti-PD-1 release. Later, the researchers developed a synergistic immunotherapy strategy by modifying LMW-HA (50 kDa) with 1-methyl-dl-tryptophan, which is the inhibitor of the immunosuppressive enzyme. Their outcomes suggest that an LMW-HA microneedle strategy may engender the sustained release and promote retention of checkpoint inhibitors in the tumor milieu (Fig. 6**B-D**) [75].

3.1.3. Pullulan-based nanomaterials

As a natural biopolymer stemming from fungus-like yeast, pullulan is a readily water-soluble neutral polysaccharide with potently pro-inflammatory attributes [76]. Previous studies have shown that pullulan can induce the generation of pro-inflammatory cytokines, such as IL-6, IL-8, IL-1β, and TNF-α, in human blood cells [77]. Further, pullulans play a pivotal role in macrophage-mediated cancer cell apoptosis via contact with macrophages and subsequently elicit TRAIL expression at a relatively stronger level in comparison with lipopolysaccharide (LPS) induction [78]. Wang et al. determined the potent pro-inflammatory effect of pullulan along with its acidic and alkaline derivates. Their outcomes revealed that pullulan can modestly activate TLR-mediated MyD88-dependent type I IFN and NF-κB signal pathways *in vivo*, inducing diverse proinflammatory cytokines. And the alkaline derivates of pullulan exhibited remarkable proinflammatory capacity [76]. Additionally, by upregulating various proinflammatory cytokines in DCs in a concentration dependent manner, pullulan shows giant potential to induce the type I IFN and NF-κB signaling pathways and is thereby useful for drug delivery without adjuvants, especially by harnessing its promising effect in eliciting anti-tumor immune responses.

To further confirm the anticancer immunity of pullulan, one group conducted studies on evaluating the Th1 and Tc1 immune responses of pullulan *in vivo*. They found that pullulan can induce the maturation of DCs in spleen and tumor draining lymph node, promoting the OVA-specific T cell activation and the T cell migration toward the tumor [79]. In this regard, pullulan can be further exploited to deliver drugs to overcome drug-resistance of cancer cells. Guo et al. conjugated urocanic acid to pullulan, forming a pH-sensitive pullulan-based nanosystem for delivering Adriamycin. Such nanoparticles could efficiently enhance accumulation and retention of the cargos and induce the immunity responses *in vivo* [80].

In another study, pullulan was applied to generate cholesterol-bearing pullulan (CHP), serving as self-assembly nanogel for delivering antigen to cells in the lymphatic system that will elicit immune responses [81]. Remarkably, such CHP nanogel can act as a protein-delivery vehicle and deliver antigen to lymph nodes, activating both cellular and humoral immunity. The results showed the antigen was delivered to APCs with a high cross-presentation ability and the nanocarrier exhibited a very strong cytotoxic T lymphocytes activation.

3.1.4. Alum-based NPs

Trivalent aluminum salts, generally referred to as alum, is another candidate vaccine adjuvant in nature. Alum consists of crystal aluminum hydroxide as small primary particles, forming aggregates of 1–20 μm in diameter [82,83]. Alum itself can mildly potentiate antigen-specific antibody responses. Although alum-mediated induction of antigen-specific T cell responses hinges on DCs and is rested with MyD88 and uric acid, alum can still reinforce antigen-specific antibody responses of the animal model deficient in the TLR adaptors MyD88 and TRIF [84]. Flach et al. reported that alum is independent of inflammatory bodies and membrane proteins. It can directly engage DC plasma membrane lipids with considerable force. Subsequent lipid sorting may activate the abortion phagocytosis response, resulting in antigen uptake. The activated DCs have no further connection with alum, showing high affinity and stability with $CD4^+$ T cells through the adhesion molecule intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen 1 (LFA-1) [85].

Recently, Moyer et al. discovered a novel immunological mechanism of alum. They designed immunogens that could tightly bind alum via the site-specific introduction of repeating phosphoserine (pSer) peptide–polymer affinity labels. The results demonstrated that pSer-immunogen and alum complexes form NPs capable of delivery to the lymph nodes and trigger B cell activation via multivalent and targeted antigen display. The B cells are activated after directly ingesting antigen-modified alum granules through upregulated antigen treatment and presentation pathways [86]. In this regard, alum can be modified to both deliver antigen in particulate forms and realize ongoing antigen delivery to lymph nodes through engineering the binding of immunogens to alum particles via the site-specific introduction of phosphate-bearing peptide linkers [86]. Interestingly, Li et al. found that the reduction of the particle size of alum could lead to enhanced adjuvanticity *in vivo*, indicating that alum NPs can elicit even stronger antigen-specific antibody response than conventional alum microparticles [87].

3.1.5. Poly(lactic-co-glycolic acid) (PLGA) nanoparticles

Poly(lactic-co-glycolic acid) (PLGA) is one of the most frequently cited polymers in the field of biomaterials. PLGA nanoparticles are often used for the delivery of drugs and other compounds into the body as they are biodegradable, safe carriers. As such, the impact of this polymer on the native immune system has been a topic of interest among researchers. PLGA has the unique ability to stimulate both DCs and macrophages, two of the main cells in the immune system. DCs are a key player in the innate immune system as they are the main antigen-presenting cells to CD4 + and CD8 + T cells [88]. They are critical for creating an adaptive immune response to vaccines through uptake of antigens, migration to lymph nodes, and then activation of naive T cells which subsequently stimulates antibody-generating plasma cells. The dysregulation of DC function has been implicated in autoimmune diseases and the pathogenesis of diseases of the skin, intestine, lung, and brain, as well as in atherosclerosis [89]. Several types of DCs are implicated in the pathogenesis of systemic lupus erythematosus (SLE). Inflammatory 'slanDCs'—dendritic cells that express 6-sulfo N-acetyllactosamine (slan) instead of cutaneous lymphocyte antigen (CLA)—accumulate in the skin and cause cutaneous lesions. Future work could explore methods to selectively block slanDC migration to the skin using biomaterials to decrease the burden of lupus rash. In addition, DCs can be harnessed to ini-

tiate anti-tumor immunity as part of immunotherapy by delivering tumor antigens to DCs [90].

In a comprehensive study, Park et al. evaluated the effect of five different biomaterials, including PLGA, on DC maturation [91]. The investigators recognized that therapeutics such as vaccines rely on the enhancement of the protective immune system and biomaterials can be used in combination with adjuvants to have a synergistic immune response. Immature DCs (iDCs) incubated with PLGA for 24 h displayed dendritic processes similar to those of mature dendritic cells (mDCs). The iDC phenotype was maintained following incubation with natural alginate, agarose, and hyaluronic acid films. PLGA and chitosan were also found to support allosteric T-cell proliferation and resulted in DCs with higher expression levels of CD80, CD86, CD83, and HLA-DQ. Incubation with PLGA significantly increased the levels of pro-inflammatory TNF-α and IL-6 by the DCs. The differential effects of these biomaterials on other DC properties including endocytic ability, apoptosis, and NF-κB activation were also explored in this study. In addition, the functionalization of PLGA has been found to be able to influence macrophage reprogramming and also the depletion of tumor-associated macrophages; however, these immune system influences are made possible by the adaptability of PLGA to be functionalized and not the native polymer itself [92,93].

An important consideration for PLGA, as with other synthetic polymers, is that there can be variations in the formulation depending on the manufacturer's synthesis route which may impart minor changes to the properties of the polymer. For example, PLGA can be prepared with various different catalysts. Minor variations in polymer structure and properties could potentially lead to variations in the degree of a certain influence, such as immune system modulation, that the polymer displays. Nevertheless, the high reproducibility and ability of synthetic polymers to be produced on a large scale overshadow these potential minor differences.

3.1.6. Poly(beta-amino ester) (PBAE) particles

Poly(β-amino ester) (PBAE) is a synthetic polymer known for its pH-sensitivity and biodegradable properties. Interestingly, different physical configurations of PBAE can lead to varying effects on immune cells [71]. Investigators at the University of Maryland recently explored the intrinsic immunogenicity of PBAEs as a function of the degree of polymer degradation and polymer form (free vs. particles). The effects of a prototypical form of PBAE, Poly 1, was tested at varying molecular weights in either the free or particulate form. Primary CD11 + DCs were isolated from spleens of C57BL6 mice and treated with varying molecular weights of intact, free PBAE or microparticulate PBAE.

Notably, particulate PBAE led to the increase of DC release of costimulatory markers in MW-dependent manner, while free PBAE had no effect on DC stimulation. The inability of free PBAE to stimulate DCs may be due to the fact that DCs are unable to efficiently internalize the soluble and relatively low MWs materials. DC phagocytosis is able to more efficiently engulf larger, particulate antigens compared to the pinocytosis internalization of smaller antigens. This highlights the fact that the molecular weight or physical form of a polymer can have varying degrees of immunomodulatory effects.

3.1.7. Dendrimers for immune activation

Dendrimers are branched nanostructures that can have a variety of functional surface groups and possess a wide range of properties [94]. They are composed of an anchoring core, with symmetric interior branches, which can have multiple branching points leading to an exponential number of terminal functionalized branches. They can be complexed with bioactive compounds by physical linkages or entrapment into the dendrimer frame to form therapeutic immune conjugates. This can assist in eliciting an enhanced immune stimulation response in the body. Recent studies have found that positively charged dendrimers can act as vaccine carriers and elicit increased cytokine production [95].

Polyamidoamine (PAMAM) is a commonly cited hyperbranched dendrimer material composed of two ethylenediamines joined by methyl acrylate that was first introduced in 1985 [95]. The identity of the functionalized branches at the end of PAMAM branches determines the dendrimer's charge—terminal hydroxyl (–OH) groups confer a neutral change, cationic amino ($–NH_2$) groups produce a positive charge, and carboxyl (–COOH) termini have a negative charge [96]. The term dendrimer "generations (G)" refers to the number of repeated branching cycles performed during its synthesis; G1, G2, G3 and G4 dendrimers with four core branches have 8, 16, 32 or 64 terminal functional group branches, respectively [94].

Dendrimers are highly versatile synthetic polymers. They can vary vastly due to their ability to be functionalized with different terminal groups. Dendrimers have a wide size range from about 1 nm in diameter for the smallest PAMAM G0 dendrimers up to approximately 13 nm for PAMAM G10, with the diameter increasing linearly for subsequent generations [97]. The conjugation of dendrimers with different functional groups is a contributing factor to their ability to interact with immune cells and elicit an immune response. G4 amine- and lipid-functionalized PAMAM was found to increase CD11b and CCR2 overexpression in primary CX3CR1-GFP murine microglia *in vitro*. Microglia are the resident macrophage cells of the central nervous system (CNS), suggesting that this functionalized dendrimer may cause neural immune cell activation if it were to cross the blood brain barrier [98]. Overall, the modulation of the terminal branches of dendrimers can be taken advantage of to obtain a polymer with the specific properties that will suit the final application of the dendrimers.

3.1.8. Synthetic polymers and lipids for STING activation

In recent years, there has been rising interest in generating a potent T cell response through activation of the stimulator of interferon genes (STING) pathway, as previously discussed in section 3.1.1 and depicted in Fig. 5, for cancer vaccine strategies to thwart STING-induced antitumor immunity. However, this was typically achieved through the conjugation of adjuvants, which can increase nanoparticle size, deterring effective accumulation in lymph nodes and cellular uptake. To overcome these challenges, researchers have developed various synthetically engineered polymer and lipid compounds with STING binding and activating properties for the delivery of antigens.

Notably, the Gao group has developed synthetic polymer compounds capable of generating a cytotoxic T cell response and activating type I IFN-stimulated genes. Among them, the pH-sensitive polymer with a cyclic seven-membered ring (PC7A) was first reported in 2017, and when loaded with a model antigen ovalbumin (OVA), was shown to induce an OVA-specific cytotoxic T cell response [99]. Furthermore, in a more recently published study, Gao et al. demonstrated significant tumor growth inhibition and enhanced survival in two different *in vivo* tumor models using cGAMP-loaded PC7A NPs to induce phase condensation of STING [100]. The PC7A polymer was found to generate sustained STING activation for over 48 h by binding to STING with high affinity.

In another innovative approach, the Anderson, Langer, and Doloff groups developed a library of over 1,000 lipids that could be synthesized through a one-step, three-component reaction. The researchers found that lipids with unsaturated lipid tails, dihydroimidazole linkers and cyclic amino head groups could activate the MyD88/RLR-independent STING pathway to induce APC maturation, and moreover, could be condensed with mRNA to form lipid nanoparticles (LNPs) for cancer treatment. The efficacy of the sys-

tem was demonstrated in a melanoma tumor model, and mice treated with the top-performing LNPs were found to have lasting tumor immunity up to 21 days, even against a second tumor challenge. The LNPs also had improved intracellular STING activation due to their ability to be internalized through NP-mediated endocytic mechanisms [101].

Taken together, these studies show that polymeric and lipidoid carrier-mediated activation of the STING pathway can generate a strong enough cytotoxic T cell response to inhibit tumor growth. There is potential to explore the synergistic combination of such treatments in conjunction with other therapies such as ionizing radiation for more effective eradication of large and established tumors [102]. Furthermore, it is evident that future work in synthetically engineered polymers and lipids should likewise implement the systematic combinatorial screening of synthetic polymer and lipid formulations as an efficient strategy to identify effective STING-activating carriers for cancer nanovaccine development.

3.2. Anti-inflammatory materials

Conventional inflammatory treatment strategies mainly involve steroidal and non-steroidal anti-inflammatory drugs (NSAIDs), both of which possess non-negligible side-effects [49]. A great deal of newly emerging nanomaterials that may exhibit anti-inflammatory activities has attracted extensive attention in recent years. These promising nanomaterials themselves can exert an anti-inflammatory effect by suppressing the immune pathways *in vivo* and offer a nanotechnology platform for the reformulation of immunosuppressive agents by improving solubility, providing fine targeting, mitigating side effects and offering alternative less-invasive delivery routes [103].

3.2.1. Cell-free DNA (cfDNA)-binding dendrimers

As discussed in section 3.1.7, PAMAM dendrimers can induce a pro-inflammatory effect through their conjugation with immune-stimulatory terminal groups or complexation with immune adjuvants, but research has also shown that the scavenging ability of these dendrimers to bind cell-free DNA (cfDNA) can lead to reduced systemic inflammation. Circulating cfDNA belongs to the broad category of damage associated-molecular patterns (DAMPs) which stimulate toll-like receptors (TLRs) and activate an inflammatory cascade.

PAMAM-G3 was recently found to act as a nucleic acid binding polymer (NABP) and bind pro-inflammatory cfDNA in mice bearing KPC4580P luciferase expressing murine pancreatic cancer cells in their spleens [104]. Mice bearing tumors treated with 20 mg/kg intraperitoneal PAMAM-G3 for three weeks were found to have a significantly decreased number of metastases to the liver and a significant decrease in their cfDNA levels. The binding of DNA to toll-like receptor 9 (TLR9) induces inflammation via the NF-κB pathway. TLR9 activation also increased the expression of genes for adhesion molecules and inflammatory cytokines that have been shown to contribute to the epithelial-mesenchymal transition and metastatic spread of cancer cells [105,106]. The study also collected serum from healthy human individuals and patients with pancreatic cancer (PC). The serum of PC patients significantly increased the TLR9 activation of HEK-Blue TLR9 reporter cells compared to serum of healthy individuals; however, inoculation of PC patient serum with 20 ug/mL of PAMAM-G3 significantly attenuated the TLR9 activation. A reduction in TLR activation has several downstream effects including the prevention of the inflammatory NF-κB activation. This provides evidence that the PAMAM-G3 dendrimer solutions are able to interact with cfDNA or cfDNA-protein complexes that are responsible for activating TLR9 receptors and attenuate them to reduce metastatic spread.

The ability of PAMAM-G3 to bind cell free nucleic acids has also been found to alleviate the excess immune stimulation occurring in autoimmune diseases such as systemic lupus erythematosus in mice [11,12]. In a study evaluating the efficacy of PAMAM-G3 in the context of autoimmunity, NZBW F_1 mice treated with PAMAM-G3 showed a reduction in their cutaneous lupus erythematosus-like phenotype and MRL^{lpr} mice treated with PAMAM-G3 had a decrease in their serum levels of circulating anti-nuclear and anti-dsDNA antibodies (Abs) compared to untreated and PBS-treated mice [12]. Anti-nuclear and anti-dsDNA Abs exacerbates autoimmunity in the lupus-prone animals, and they serve as markers in the diagnosis of lupus in human patients. These studies highlight the potential for PAMAM-G3 treatment to ameliorate the negative side-effects associated with inflammation in the setting of cancer, autoimmune diseases, and other conditions in which inflammation is detrimental.

3.2.2. Chitosan for anti-inflammatory applications

Aside from serving as a mucoadhesive nanovaccine and antitumor vaccine for cancer immunotherapy, CS has also been widely applied for anti-inflammatory treatment. Previous research has validated that chitosan oligosaccharides may exert the anti-inflammatory effects by suppressing the activation of the LPS-induced p38 MAPK/ERK1/2 and NF-κB signaling pathways, resulting in a decrease in the mRNA levels of E-selectin and ICAM-1 [107]. CS can also serve as a chemoattractant to neutrophils, as evidenced by the work of Simard et al. [70]. In comparison with other neutrophil chemoattractants, CS cannot elicit generation of a superoxide burst or degranulation, suggesting that it may foster the wound-healing phenotype among neutrophils.

Furthermore, CS has been exploited as a matrix scaffold. Rao et al. developed a bioactive and biodegradable material, neurotrophin-3 (NT3) loaded-chitosan to elicit robust *de novo* neural regeneration. The NT3-chitosan scaffold could effectively prevent the infiltration of inflammatory cells and attract the proliferation, migration, and differentiation of endogenous NSCs, forming nascent relay neuronal networks to transmit ascending and descending neural signals to proper targets [108]. In this work, CS with favorable anti-inflammatory properties is a promising natural and non-toxic material for regenerative treatment. After implantation, this CS-based delivery system also released the neurotrophic factor into the milieu, in a relatively long-term and controlled manner.

CS has also been harnessed for periodontal disease treatment in human gingival fibroblasts. Martin et al. designed CS NPs to pack minocycline, an anti-inflammatory tetracycline that is delivered locally in the periodontal milieu [109]. Their outcomes showed that such a nanosystem can significantly downregulate levels of inflammation-related markers and possesses the potential to be applied for the periodontal disease therapy, combined with the capacity of targeting intracellular agents and robust anti-inflammatory effects. In addition to its application in perioceutics, CS has also been used in conjunction with hyaluronan to develop a novel wound healing material, as shown by Tamer et al. The N acetylglucosamine (NAG) present in CS is a dominant component of dermal tissue, which is crucial for exerting anti-inflammatory functions. This engineered composite material was also boosted with edaravone, an anti-inflammatory drug, and displayed substantial promotion of the wound healing process in rat skin [110].

3.2.3. High molecular weight hyaluronic acid (HMW-HA)

As discussed in section 3.1.2, HMW-HA can bind CD44, TLR-2, and TLR-4, thereby facilitating anti-inflammatory effects within the cell. Additionally, it can also inhibit pro-inflammatory cytokine levels via interplay with ICAM-1 via the downregulation of NF-κB and I-κB kinase (IKK), an enzyme complex upstream of the NF-κB

signaling cascade. It has also been reported that the binding of HMW-HA to the CD44 receptor can form a protective layer to coat the cell membrane, blocking cell death receptors and restraining cell apoptosis [111].

In contrast to LMW-HA, HMW-HA can more effectively relieve symptomatic pain caused by osteoarthritis (OA) due to its ability to prevent TNF-α induced suppression of chondrogenic differentiation with no effect on cell viability [112]. Of note, the high expression of matrix metalloproteinase 13 (MMP13) plays a pivotal role in the progression of OA cartilage. Injection of HMW-HA has been clinically leveraged as a symptomatic non-surgical therapeutic regimen of OA [113]. Furuta et al. uncovered that the interaction between HMW-HA and CD44 can inhibit TNF-α-induced MMP13 expression by downregulating the MAPK/AP-1 axis. In addition, HMW-HA exerted protective effects against matrix degradation by modifying TNF-α-mediated signaling pathways [114]. Wang and colleagues also investigated the effect of HMW-HA on the gene expression of various inflammatory cytokines in fibroblast-like synovial cells (FLS) in patients with OA. They found the gene expression of iNOS, IL-8, and TNF-α was downregulated in unstimulated FLS. Thus, blocking the CD44 receptor with the corresponding antibody may inhibit the downregulatory effects of HMW-HA [115].

The NF-κB and TNF-α pathways have also been explored as targets for cancer treatment. To this end, Wei et al. fabricated a cholesteryl-hyaluronic acid (CHA) nanogel to conjugate curcumin (CUR), which is a promising anti-inflammatory agent [116]. This nanosystem not only exhibited prime solubility and sustained drug release under physiological conditions but also induced apoptosis of tumor cells, inhibiting the expression of NF-κB and TNF-α cellular targets like free CUR. The overall results demonstrated that this CUR-CHA nanogel could produce up to 13 times tumor inhibition in terms of its excellent cellular permeability and anticancer activity [116].

HMW-HA-functionalized smart multiwalled carbon nanotubes (MWCNT) have also recently been reported with great potential to serve as tumor-targeting drug delivery agents. Hussain et al. revealed that the HA functionalization of MWCNT could mitigate postexposure lung inflammation, fibrosis, and mucus cell metaplasia [117]. Following exposure to this nanosystem, cocultures of fully differentiated bronchial epithelial cells and human lung fibroblasts showed pronounced reduction in injury, oxidative stress, and pro-inflammatory gene expression, implicating HA functionalization in the reduction of MWCNT-elicited epithelial injury.

3.2.4. Heparin-based nanomaterials

Composed of 1,4 linked disaccharide repeating units of uronic acid and glucosamine residues, heparin has been broadly utilized as an anticoagulant and antithrombotic drug [53]. More recently, some researchers have also incorporated heparin into nanoformulations for cancer treatment in view of its unique biological properties, such as nontoxicity, anticancer activity in the angiogenesis and metastasis processes [118,119]. Although primarily employed for its anticoagulant and anticancer attributes, heparin has also long been known to possess anti-inflammatory activity.

Heparin plays a pivotal role in the immune system due to its capacity to interact with pro-inflammatory cytokines and chemokines. In general, the anti-inflammatory effects of heparin are associated with their ability to interfere with almost every stage of leukocyte transmigration, incorporating the initial attachment and rolling of leukocytes on inflammatory cells, endothelial cells binding to chemokines to galvanize leukocytes, and activating stable adhesion of leukocytes to the endothelium [120]. Furthermore, at the molecular level, there is evidence that heparin may exert its anti-inflammatory effects via the transcription factor NF-κB. NF-κB can be activated by many agents, including LPS, cytokines, UV irradiation, free radicals, oxidative stress, and viral infection [121]. Intriguingly, low molecular weight heparins (LMWHs), which are products of depolymerization of unfractionated heparin, have also been demonstrated to possess the ability to target disparate aspects of the inflammatory process [122]. For example, in an early clinical trial, enoxaparin, a commonly used LMWH, displayed promising outcomes in reducing the release of

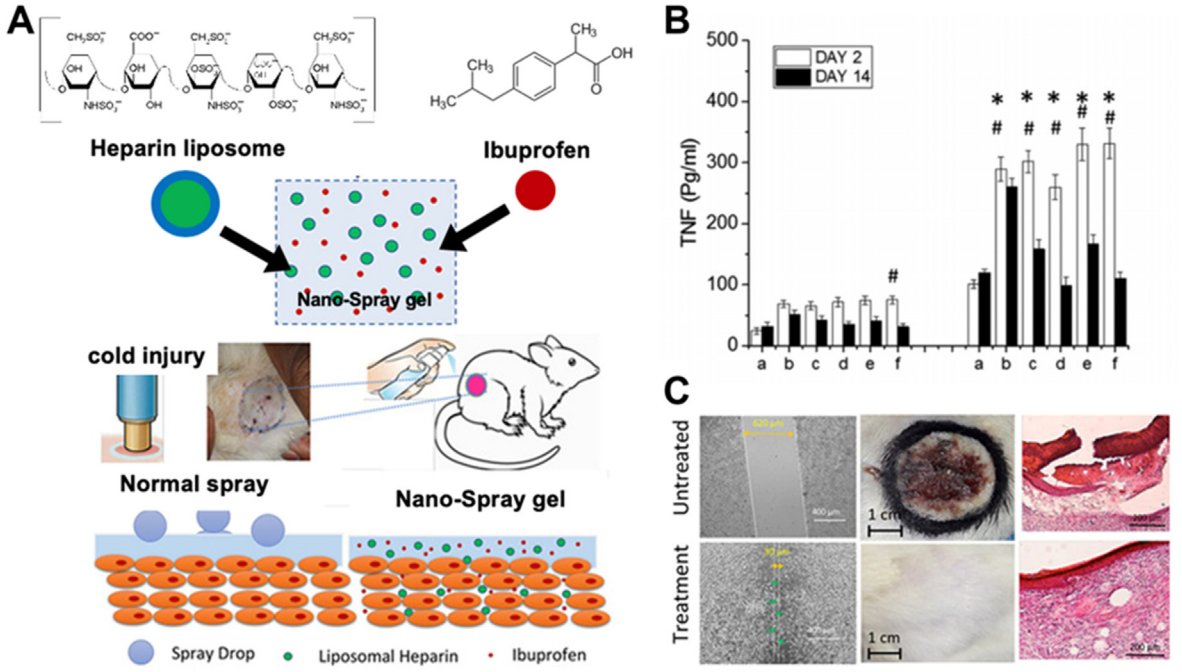

Fig. 7. Heparin encapsulated topical "Nano-spray gel" liposomal formulation guarantees rapid on-site treatment of frostbite injury via inflammatory cytokines scavenging. (A) Schematic illustration of the fabrication and mechanism of the "Nano-spray gel". (B) The level of TNF-α in the wound site and blood circulation (a: No Frostbite, b: Frostbite induced-untreated, c: Sulfadiazine Ointment, d: Blank group, e: Heparin liposomes, f: Heparin liposomes and Ibuprofen). (C) Morphometric and histopathological images of frostbite healing dynamics in rats. Adapted from Vaghasiya et al. 2019 [126].

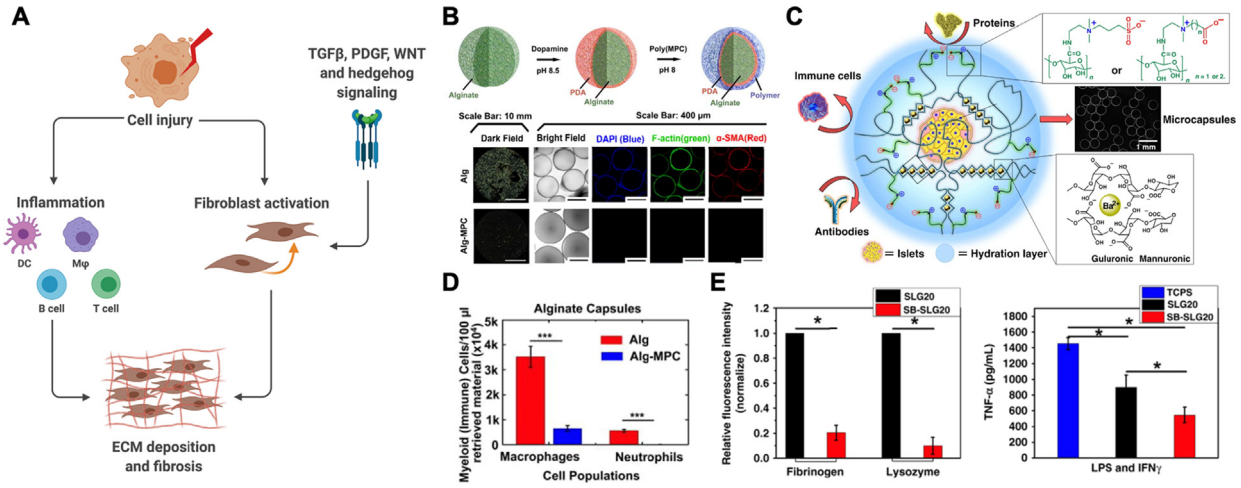

Fig. 8. Zwitterionic coatings endow anti-fibrotic properties. (A) Basic mechanisms of fibrosis include inflammation and growth factor-driven fibroblast activation, leading to ECM deposition and myofibroblast build-up [6,142]. (Created with BioRender.) (B, D) Poly(MPC)-coated alginate microcapsules exhibit reduced immune cell activation [129]. (C) Islet-encapsulating SB-alginate microcapsules. (E) FITC-labeled fibrinogen and lysozyme on surfaces of hydrogel microcapsule quantified by ImageJ. (F) TNF-α secretion from macrophages cultured on various surfaces [141].

inflammatory cytokines and suppressing the bronchoconstriction induced by asthma [123]. Another application of heparin is in peritoneal inflammation; Lever et al. reported that locally administered heparin results in anti-inflammatory effects at the site of inflammation in an *in vivo* model, thereby limiting the degree of cell influx to the area [124].

Recently, Al-Khoury et al. used heparin in its polyanionic form complexed with naproxen, an NSAID, to generate polymeric nanoparticles via polyelectrolyte multilayer (PEM) coatings. Using THP-1-derived macrophages to study short-term anti-inflammatory activity, they found that the PEM nanoparticles that contained heparin could reduce cell adhesion and IL-1β secretion compared to the polystyrene sulfonate control group. After 15 days, the nanosystem reduced foreign body giant cell formation, suggesting long-term anti-inflammatory effects. The nanoparticles could also be taken up by macrophages, implicating a release of naproxen via the digestion of nanoparticles in the lysosomal compartment. Hence, nanoparticles with PEM surface coatings of heparin and naproxen have the potential to mitigate the foreign body reaction (FBR) after implantation, yielding long-term functionality of implants [125].

Further, Vaghasiya and colleagues developed a topical "nanospray gel (NSG)" formulation with a combination of liposomal heparin sodium and ibuprofen (Ibu) for rapid relief of frostbite injury in hypothermia (Fig. 7**A**). Notably, heparin liposomes presented significant healing of the wound *in vitro*, and exerted modulation of inflammatory cytokine mediators (IL-6, TNF-α, IL-10, IL-4) at the wound site and in blood circulation to foster frostbite healing (Fig. 7**B-C**) [126].

3.3. Immuno-evasive materials

Aside from immune activation or downregulation, materials that are able to evade the immune system have also begun to gain interest in recent years. In particular, fibrosis has been the main target of many efforts to design carriers that can avoid detection by the immune system. Fibrosis, or fibrogenesis, is the formation of scar tissue in response to a trauma or injury through an accrual of collagen-rich extracellular matrix (ECM) molecules. This is typically due to an irritant that results in sustained production of stimulatory molecules such as fibrogenic cytokines, chemokines, enzymes, or growth factors, notably transforming growth factor beta (TGF-β), a key signaling molecule in wound-healing macrophage activation [6]. These molecules then induce a chronic and uncontrolled build-up of these ECM molecules that destroy healthy parenchymal tissue and remodel it with connective scar tissue (Fig. 8**A**) [6,127]. Although this is typically meant to serve as a reparative process at the end of the chronic inflammatory pathway, the prevention of fibrosis is important for several applications, including but not limited to fibrotic diseases such as pulmonary, liver, and cystic fibrosis, all of which can lead to fibrosis-induced organ failure and contribute to as much as 45% of all deaths in the developed world [128]. It is also relevant for treating chronic wounds such as diabetic ulceritis.

Additionally, biomaterial-induced fibrosis poses another challenge relating to collagen accumulation around implanted devices. Many commonly used implanted devices and materials face limited clinical utility due to this formation of a fibrous capsule, which can lead to host rejection and downstream complications such as device failure and tissue distortion [129,130]. These include silicone, poly(ethylene glycol) (PEG), poly(2-hydroxyethyl methacrylate) (PHEMA), and titanium, among other polymeric, metallic, and ceramic materials [131]. This foreign-body reaction (FBR) is commonly treated with systemic injections of corticosteroids or NSAIDs after implantation, which can cause the development of intestinal ulcers and increase the risk of cardiovascular morbidity [130]. Thus, it is imperative to develop methods to improve wound healing processes, impart non-fouling properties (i.e., prevent non-specific protein adsorption), and mitigate foreign body responses not just with drugs but also with drug delivery devices and systems. This concept was introduced in section 3.2.4 when discussing anti-inflammatory effects of heparin, thus, to avoid repetition and provide a deeper level of analysis, we will focus on polysaccharide and zwitterionic carriers specifically capable of producing immuno-evasive responses to mitigate FBR in this section.

3.3.1. Polysaccharide carriers

Polysaccharides such as alginate, chitin, chitosan (CS), and their derivatives are commonly used for drug delivery due to their natural abundance, biocompatibility, and controlled release and pH-responsive properties, among other therapeutic benefits. See sections 3.1.1. and 3.2.2. for further information about the properties of these polysaccharides.

Alginate has been investigated as both a carrier for fibrotic disease treatment and a coating for implantable devices, such as allogeneic cell transplants, due to its potential anti-fibrotic and

immune protective properties [132–134]. However, on its own, it is still limited as positive results in rodent models have failed to translate in human clinical trials [134]. In 2016, Anderson and colleagues used a combinatorial approach to determine the ideal triazole-modified alginate hydrogel composition that was capable of reducing foreign body response [135]. In the presence of dicationic solutions, alginate can form hydrogels, which is a desirable formulation for many biomedical and drug delivery applications due to its tunability and biocompatibility. It is also important to note that the Anderson group previously determined that size and shape of the microspheres influence the FBR in rodents and non-human primates [136]. They found that these triazole-modified alginate hydrogels reduced cathepsin activity, which are lysosomal proteinases implicated in fibroblast-induced chronic inflammation [137]. Additionally, they found reduced macrophage (CD68, CD11b) recruitment *in vivo*, with up to 60% reduction in α-smooth muscle actin (α-SMA), a marker of myofibroblast formation, and significant decreases in collagen content on the top three leading chemically-modified formulations compared to the PRONOVA^{TM} SLG20 control in non-human primates.

Anderson and colleagues continued to expand upon this work two years later, by using the leading triazole-modified alginate formulations to encapsulate glucose-responsive allogeneic islet cells in a non-human primate study. Remarkably, there was a 45% reduction in CD68 and CD11b-positive cells after one month with the lead formulation compared to SLG20, with sustained significance in reduction even after four months post-implantation in the omental bursa of macaques. Additionally, there was no significant loss in functionality of the islets in terms of glucose-triggered insulin secretion, at four months post-implantation compared to one month [134]. A similar study by the Group for Functionalized Biomaterials at EPFL demonstrated that ketoprofen-grafted alginate microcapsules can likewise facilitate transplantation of insulin-secreting cells in a mouse model while reducing pericapsular fibrotic overgrowth [138]. It is believed that modulation of upstream macrophage activation leads to reduced myofibroblast recruitment, which contributes to fibrosis and FBR (Fig. 8**A**).

Modification of CS has also been explored as an alternative carrier for anti-fibrotic applications. Zheng et al. showed that grafting high molecular weight methoxy poly(ethylene glycol) (MPEG) onto CS could improve the anti-fibrotic effects of chitosan alone by preventing protein adsorption onto the surface due to the interfacial hydration layer and the steric stabilization (a combination of the volume restriction effect, the loss of configurational entropy, and osmotic repulsion). Specifically, they modified alginate/CS/alginate/CS-g-MPEG ($ACAC_{PEG}$) multilayer hydrogel microcapsules with the graft copolymer chitosan-g-MPEG (CS-g-MPEG), and measured protein adsorption using IgG as a model protein. CS-g-MPEG2K resulted in a 61% reduction of IgG adsorption compared to the chitosan surface [139]. This study suggests that there is further potential to explore the effects of graft copolymers on polysaccharide carriers in order to improve protein repulsion effects to reduce non-specific adsorption of fibrogenic molecules and FBR.

In 2015, Zhu et al. demonstrated that addition of the TGF-β inhibiting aptamer, S58, in a thermo-sensitive CS gel downregulate α-SMA and collagen-I, leading to suppression of conjunctival fibroblast proliferation in a rat glaucoma model [140]. Importantly, both chitosan alone and CS-S58 were shown to reduce recruitment of lymphocytes and macrophages and minimize fibroblast infiltration and collagen deposition, compared to the untreated control.

These results demonstrate the value of combinatorial testing for identification of promising candidates and importantly, the further potential of modified polysaccharide-based microspheres for anti-fibrotic applications, particularly in islet cell transplantation for type I diabetes and other hormone-deficient diseases. Combinations of CS and alginate may also warrant further exploration, such as the $ACAC_{PEG}$ multilayer hydrogel microcapsules formulated by Zheng et al [139].

3.3.2. Zwitterionic polymers

In recent decades, there has been rising interest in the use of zwitterionic polymers to reduce fibrotic events. Zwitterionic polymers are those that carry zwitterions such as phosphorylcholine, sulfobetaine (SB), and carboxybetaine, which possess equal amounts of cationic and anionic groups to form an electrically neutral material. They have been studied for their low or non-fouling ability, with poly(carboxybetaine) (PCB) and PCB-methacrylate (PCBMA) being the most popular, as they have been shown to form protective hydration shells through electrostatic interactions, thus mitigating cell overgrowth [8].

In 2013, Jiang and colleagues used PCBMA hydrogels to induce much lower cell adhesion *in vitro* than PHEMA and to impart ultra-low fouling properties when implanted subcutaneously in a mouse model for three months, as shown by the increased uniformity of collagen density and angiogenesis. The authors hypothesized that the increased angiogenesis in surrounding tissue was due to the observed increased recruitment of anti-inflammatory, pro-healing macrophages and decreased levels of pro-inflammatory markers in tissues near PCBMA hydrogels as compared to PHEMA hydrogels [131].

This laid the groundwork for further research into endowment of anti-fibrotic properties via zwitterionic surface coatings on biomaterials. Yesilyurt et al. demonstrated the ability to coat alginate microspheres, with mussel-mimetic zwitterionic poly(methacryloyloxyethyl phosphorylcholine) (poly(MPC)) thin films [129]. Through flow cytometry analysis, they showed that macrophage and neutrophil adhesion to the polyMPC-coated capsules were reduced significantly compared to uncoated alginate microspheres (Fig. 8**B, D**). The authors believe this reduction in immune cell recruitment would prevent fibrotic activity. Further *in vivo* analysis would be warranted to demonstrate their clinical utility.

More recently, Ma and colleagues used SB and CB to modify alginate microspheres for cell encapsulation in mice, dogs, and pigs (Fig. 8**C**). They hypothesized that zwitterionic modification of alginate would result in improved islet encapsulation in a streptozotocin-induced diabetic mouse model based on the previously discussed results from Jiang and colleagues [141]. They demonstrated that SB-SLG20 microcapsules can mitigate cellular overgrowth, evidenced by the significant reduction of two model proteins, fibrinogen and lysozyme, compared to SLG20 (Fig. 8**E**). This antifouling property is likely attributed to the strong hydration of the SB groups. Additionally, bone marrow-derived macrophages (BMDM) stimulated with lipopolysaccharide/ interferon gamma and cultured on SB-SLG20 hydrogels were shown to inhibit secretion of TNF-α, demonstrating inhibited activation of pro-inflammatory macrophages (Fig. 8**F**). Finally, cells encapsulated in SB-SLG20 maintained long-term glycemic control *in vivo* for up to 200 days. A major advantage of this rational design method of alginate modification is that it is much less expensive compared to the high-throughput approach for triazole modification by Anderson and colleagues, highlighted in section 4.1.1. Taken together, these findings indicate that zwitterionic gels and modifications of other formulations may be another promising approach to evading the immune system to reduce FBR.

4. Conclusion and future outlook

In conclusion, we have reviewed five major areas of therapeutic carriers: ROS generating, ROS scavenging, pro-inflammatory, anti-inflammatory, and immuno-evasive materials. These therapeutic effects are caused by carrier-host interactions, and as we have dis-

cussed, many of these therapeutic carriers confer multiple effects, such as anti-inflammatory and anti-microbial effects. Firstly, we have summarized the role of ROS generating and scavenging materials. Although we focused on the use of these nanocarriers for cancer therapeutics as most recently published works were concentrated in this area, many other inflammatory diseases also exhibit overgeneration of ROS, such as Alzheimer's disease, cystic fibrosis, and arteriosclerosis, all of which could benefit from the use of ROS scavenging systems. Future work should thus take advantage of the wide-ranging implications of using these ROS scavenging nanoparticles as delivery vehicles for applications beyond cancer treatment. Scavengers can also be viewed as a macromolecular drug whose properties can be tuned by molecular weight and macromolecular molecular structure for unique applications such as TME targeting based on pH-responsiveness. In that context, some of the supramolecular structures may be worth exploring. Additionally, some carriers such as those with diselenide bonds were not only capable of scavenging ROS but were also found to reduce the side effects of chemotherapy and radiotherapy, demonstrating another attractive opportunity for cancer treatment.

We also discussed natural and synthetic materials capable of mediating inflammatory pathways. Although beyond the scope of this review, factors such as size, shape, and structure of the carrier have also been shown to affect immunomodulation and thus should be studied in greater detail and taken into consideration when designing carriers. It is also important to note that the underlying mechanisms for these effects are not entirely understood, especially with regard to the specific immune pathways. For example, while the effect of singular PAMAM generations on immune molecules has been studied by researchers, more studies to better understand these effects are needed in the field of biomaterials. Due to the immense variability that exist in the academically available dendrimer library, understanding the mechanism by which PAMAM dendrimers are able to elicit immune responses requires a systematic approach where variables such as dendrimer charge, generation and terminal functional groups, are carefully controlled and studied.

The final category of materials reviewed was immuno-evasive carriers. As mentioned previously, combinatorial screening methods will enable testing of various combinations of modified polysaccharide-based microspheres, and identification of promising candidates for mitigating FBR as well as for therapeutic applications such as islet cell transplantation. This area also has significant overlap with anti-inflammatory materials due to the important role of the immune system in the FBR, as noted in Fig. 3.

Indeed, there still remain a wide range of carriers that create specific therapeutic effects outside the scope of the topics reviewed here, such as those with anti-viral, anti-tumor, or anti-thrombotic properties, but which may overlap with the materials reviewed in terms of functional activity and mechanism of action. Future work will further elucidate the fundamental mechanisms behind the effects and provide deeper understanding over conventional pharmacologic studies because the nanoscale carriers offer unique tunability in extracellular biodistribution and intracellular trafficking. Additionally, previous studies may have overlooked the potential effects of cationic carriers alone, by regarding them as controls without delving deeper into their potential biological effects. However, over the past ten years, researchers have been able to create a clearer and fuller picture of the materials interactions and harness their unique properties to inform the rational design of therapeutic delivery vehicles. This improved understanding will allow for the identification of other possible therapeutic carriers as well as improvements to current designs, and possible synergistic effects of combining various different materials in order to improve delivery efficacy, lifetime, and therapeutic outcome.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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