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REVIEW

Advances in Chondroitin Sulfate-Based Nanoplatforms for Biomedical Applications

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Abstract: Chondroitin sulfate (CS) is a naturally sulfated glycosaminoglycan with diverse biofunctional properties, including anti-inflammatory effects, reactive oxygen species scavenging, cartilage regeneration and immune regulation. In recent years, CS has shown significant progress in biomedical applications, particularly in drug delivery, tissue engineering, and biosensing. This paper reviews the latest advancements of CS-based nanoplatforms in the biomedical field. CS can be integrated with functional molecules to construct a variety of nanostructures, further expanding its potential applications. CS exhibits distinctive characteristics, and CS-based nanoparticles could serve as promising drug delivery vehicles in tumor therapy. Beyond their roles in drug delivery, CS-based nanoplatforms exhibit transformative potential in tissue engineering, offering promising solutions for wound repair and tissue regeneration. Additionally, CS enhances early disease diagnostics through biomarker detection, leveraging its unique molecular structure and biocompatibility. This comprehensive review explored the properties of CS-based nanoplatforms and their diverse applications, aiming to provide a reference for related research and encourage further advancements in the biomedical fields.

Keywords: chondroitin sulfate, nanoplatforms, tumor therapy, tissue engineering, biological sensing

Introduction

In recent years, natural copolymers have attracted widespread attention due to their diverse applications. These polymers can be obtained from microorganisms, plants, and animals, such as some naturally occurring anionic heteropolysaccharides.[1] Especially, polysaccharides are widely utilized in drug delivery, tissue engineering, and biosensors due to their biocompatibility, abundance and well-established modification.[2,3] Chondroitin sulfate (CS), a naturally derived polysaccharide, exhibits excellent biocompatibility, remarkable biostability and protein adsorption capacity. It has been extensively utilized in various biomedical fields.[4] CS can be biosynthesized with varying disaccharide compositions and carbohydrate backbones, resulting in different positions of sulfate groups.[5] It is composed of alternating copolymer of (β-1, 3)-linked glucuronic acid and (β-1,4)-*N*-acetyl galactosamine.[6] Based on the number and positions of sulfate groups, CS is classified into different isomers, including chondroitin sulfate A (CSA), chondroitin sulfate B (CSB), chondroitin sulfate C (CSC), chondroitin sulfate D (CSD), and chondroitin sulfate E (CSE).[7] CSA and CSC are respectively composed of disaccharides sulfated at the C4 or C6 position of the GalNAc residue. The structure of CS varies across species and tissues, exhibiting different levels of disulfated disaccharides. These include the disaccharide with sulfate groups at position C2 of GlcA and C6 of GalNAc (CSD), at positions C4 and C6 of the GalNAc unit (CSE), or at C2 of GlcA and C4 of GalNAc (CSB).[5]

Sulfation patterns are crucial to the biological activity of CS, influencing its interactions with proteins and its roles in cell signaling, tissue development and maintenance. The negatively charged sulfate groups facilitate binding to positively

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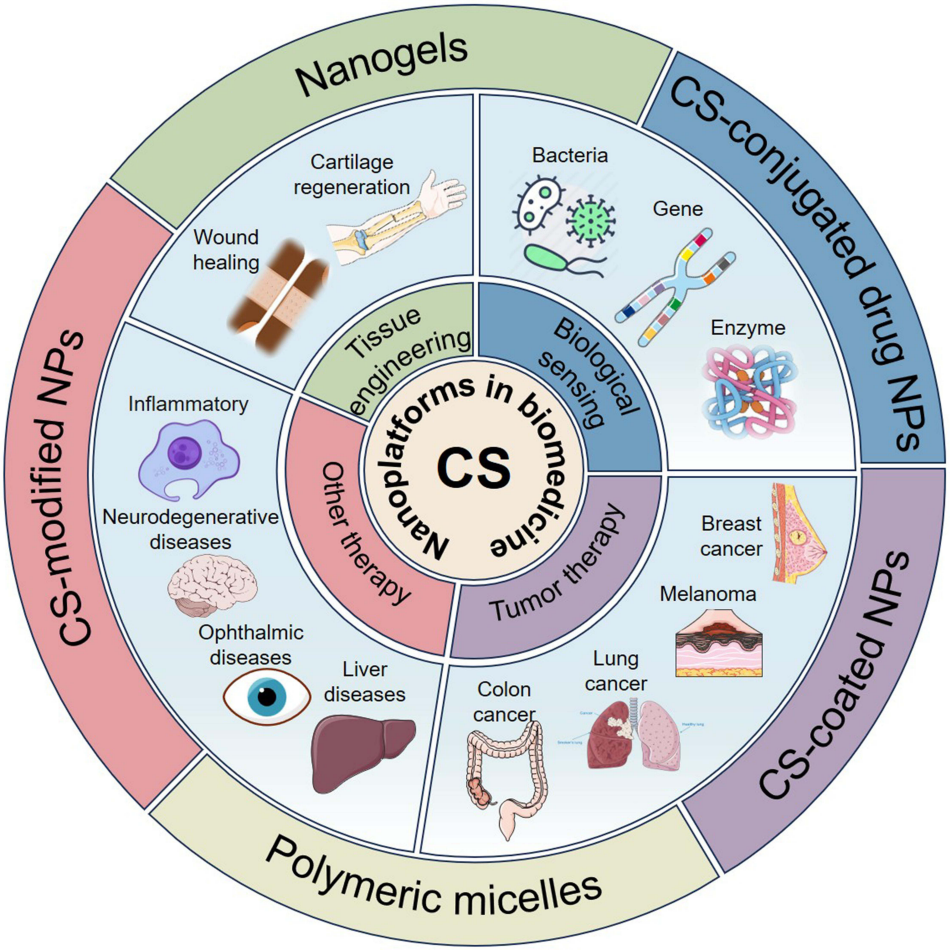
Graphical Abstract



charged regions of proteins, thereby modulating biological activity and tissue-specific functions.[8] For instance, the high density of negative charges on the surface of CS enables interactions with positively charged components of the immune system. These interactions can modulate immune cell activity and influence the release of inflammatory mediators. Thus, CS contributes to the maintenance of tissue homeostasis and resolution of inflammatory processes by regulating inflammation.[9] Additionally, CS can exert a targeting function through electrostatic interactions. It is readily recognized by the CD44 receptor, which is highly expressed on chondrocytes and tumor cells, and forms a stable hydrogen bonding network with basic amino acid residues (such as lysine and arginine) on the CD44 receptor surface via electrostatic forces. This interaction promotes receptor-mediated endocytosis, enhancing targeting efficiency.[10]

CS is present on the cell surface and within the extracellular matrix (ECM), and is covalently bound to proteins to form proteoglycans.[11,12] CS itself has anti-inflammatory and anti-osteoarthritic activities, and has become a dietary supplement approved by the United States and Europe.[13] This polysaccharide is increasingly attracting attention as a component for providing stealth functions, improving interactions with target tissues, or achieving environmentally responsive drug release in the development of functional nanomedicines.[14] CS is characterized by a series of physico-chemical properties that make it a versatile material across various scientific fields. These properties include low immunogenicity, good biodegradability and water solubility.[15]

In the biomedical fields, nanoplatforms denote engineered nanostructured systems designed for integrated diagnosis and treatment. Nanoparticles (NPs) have the ability to encapsulate and deliver biochemical signals or drugs, and enhance

their bioavailability.[16–18] NPs are considered promising carriers for drugs and imaging agents due to their ability to accumulate in therapy sites. Chaurasia et al developed novel macrophage-targeted doxorubicin (DOX)-loaded nanocapsules (NCAPs) using chondroitin sulfate (CS). These CS-anchored NCAPs were prepared with soybean oil core templates for complementary immunotherapy combined with chemotherapy in the treatment of leishmaniasis.[19] The drug delivery efficiency of traditional nanomaterials is still low, resulting in drug distribution in non-target tissues and subsequent toxic effects.[20] Furthermore, passive tumor targeting is achieved through enhanced penetration and retention effects.[21] Notably, active targeting strategies can enhance drug delivery efficiency.[22,23] CS-based nanoplatforms exhibit excellent biocompatibility, specific targeting ability to CD44 receptors, and versatile functionality for diverse biomedical applications. CS offers distinct advantages over other polysaccharide-based carriers. For instance, hyaluronic acid is susceptible to degradation by hyaluronidase.[24] This limitation can compromise targeting specificity and therapeutic efficacy. In contrast, CS demonstrates greater resistance to hyaluronidase degradation and has the ability to target both CD44 and E-selectin, enhancing its potential as a stable and effective drug delivery platform. Additionally, CS-based nanoplatforms address two major challenges faced by conventional nanocarriers: poor in vivo stability and limited tissue penetration due to physiological and microenvironmental barriers. Traditional NPs are prone to aggregation and reduced circulation time in response to fluctuations in ionic strength or pH within the physiological environment.[25] The polyanionic surface of CS minimizes serum protein adsorption and macrophage-mediated phagocytosis, thereby prolonging the drug's half-life and enhancing in vivo stability. This stability is further reinforced by electrostatic repulsion, which prevents particle aggregation.[26] Among various treatment strategies, multifunctional nanoplatforms have gained significant attention for their potential in disease therapy, offering combined capabilities such as targeted drug delivery, diagnostic imaging, and controlled therapeutic release.[27] Therefore, the development of suitable nanoplatforms for disease treatment requires a balanced approach. Prioritizing therapeutic efficacy alone while overlooking potential side effects can hinder clinical translation. For successful clinical application, both safety and effectiveness must be carefully considered and optimized.[28]

Currently, the primary methods for drug loading into NPs are as follows: emulsion-solvent evaporation, covalent conjugation, dialysis, nanoprecipitation, thin-film dispersion, supercritical fluid technology, spray drying, electrospinning, ionotropic gelation, and microfluidics. However, among these existing nanoparticle drug-loading techniques, emulsion-solvent evaporation, covalent conjugation, drug nanocrystal encapsulation, dialysis and electrostatic adsorption have shown greater applicability in CS- based nanoplatforms.[29–32] These techniques are well-suited due to the unique chemical and physical properties of CS.

CS-based formulations or composite materials have been previously summarized.[33,34] The present review highlights the recent research advancements in CS-based nanoplatforms for biomedical applications. These nanoplatforms have demonstrated remarkable potential in tumor therapy and disease treatment, particularly in anti-inflammation, owing to their distinctive physicochemical properties and biological functions. Additionally, CS-based nanoplatforms have application prospects in tissue engineering and biosensing. Finally, this review explores the challenges, difficulties, and future opportunities associated with CS nanoplatforms.

CS-Based Nanoplatform in Tumor Therapy

Conventional cancer treatments, such as chemotherapy and radiotherapy, exhibited moderate efficacy in suppressing tumor progression. However, these therapies imposed significant physical and psychological burdens on patients.[35] Despite considerable advances in diagnostic precision and treatment strategies, cancer remains a major global health challenge. Continuous innovation in treatment approaches is essential to overcome evolving therapeutic resistance and disease heterogeneity. NPs demonstrate substantial potential as drug carriers among the various emerging cancer therapeutic strategies. These NPs have proven to be promising carriers for both therapeutic drugs and imaging agents, as they can effectively target and accumulate in solid tumors.[36] The enhanced permeability and retention (EPR) effect is based on the defects of tumor vasculature and poor lymphatic drainage, which allows NPs to extravasate and accumulate in tumors.[37] The targeting specificity and retention time of NPs can be enhanced by the surface modification of nanomaterials, which is critical for tumor therapy. Currently, many nanocarriers are designed for the co-delivery of various drugs, including small chemical molecules, nucleic acids and proteins.[38,39] Small chemical molecules, such as

DOX, paclitaxel (PTX) and methotrexate, are conjugated to amphiphilic polymers using chemically sensitive bonds, leading to the creation of micelles and vesicles capable of encapsulating both hydrophobic and hydrophilic drugs.[40] These formulations exhibited synergistic effects on tumor cells. Furthermore, in combination with nucleic acids, such as plasmid DNA, small interfering RNA and microRNA, small molecular chemical drugs can be co-delivered using cationic amphiphilic polymers to synergistically target and eradicate tumor cells.[40]

CS exhibits unique characteristics that make it a promising vehicle for cancer therapy. Studies have shown that the expression levels of CD44 receptors are markedly elevated in some tumor cells and their metastases compared to normal cells.[41] CS has been proven to target the highly expressed CD44 receptors with high specificity.[42] As a carrier molecule, CS can be conjugated either covalently or non-covalently with drugs or functional molecules, thereby endowing these conjugates with targeted functionality.[43–45] These resulting copolymer-based NPs exhibited high specificity and reduced biological toxicity.[36] These conjugations of functional substances with CS vary in terms of binding mechanisms and composition, leading to a diverse range of formulations, including polymeric micelles, nanogels and CS-conjugated drug NPs.[29,46–48] Various CS-decorated nanostructures, such as dendritic macromolecules and lipid-based NPs, have been identified.[49,50] These nanoplatforms hold significant potential for tumor treatment.

Polymeric Micelles

Polymeric micelles are nanoscale structures formed by the self-assembly of amphiphilic copolymers, and have been extensively used in tumor therapy.[51] Hydrophilic CS can be chemically linked to a hydrophobic polymer, yielding an amphiphilic copolymer analogous to a surfactant. Upon reaching the critical micelle concentration, the amphiphilic polymer can spontaneously form polymer micelles in an aqueous medium, forming a well-defined core-shell architecture. The hydrophobic segments aggregate to constitute the inner core, while the hydrophilic CS chains protrude outward to form the aqueous-facing shell. Further, hydrophobic drugs could be encapsulated into the core of these self-assembled micelles (Table 1). This form has been shown to enhance the solubility of target drugs and concomitantly increase their stability within the internal tumor environment through the steric hindrance effect.[52] Polymeric micelles have been demonstrated to prolong the duration of drug circulation, reduce clearance rate, increase half-life and enhance the biodistribution of anticancer drugs.[53] CS and deoxycholic acid (DOCA) were successfully conjugated through adipic dihydrazide (ADH)-mediated amidation, forming a promising drug carrier CS-DOCA. By adjusting the degree of substitution of DOCA, the drug loading and release rate can be greatly influenced. As the degree of substitution increased, the cellular uptake and cytotoxicity of the self-assembled NPs were increased in MCF-7 cells.[54] Wu et al prepared CS-DOX to encapsulate berberine (BBR). This co-delivery system equipped with DOX and BBR could effectively inhibit breast cancer growth and metastasis.[15] Gaber et al co-encapsulated etoposide and all-trans RA within amphiphilic zein-CS copolymeric micelles, demonstrating an effective dual-drug delivery platform for breast cancer targeted therapy.[55]

In addition to the passive EPR effect, polymer micelles modified with targeted substances on their surface can specifically bind tumor cells, thereby achieving active targeting.[74,75] CS-based polymeric micelles target the CD44 receptors on cancer cells.[76,77] For example, Yu et al prepared CS-based NPs (CS-His), which can target the tumor cells and improve the efficiency in killing the HepG2 cell line.[56] Luo et al developed a dual-drug delivery system by co-encapsulating retinoic acid (RA) and DOX into CS-DOCA NPs. The engineered NPs demonstrated hepatic-targeting capability and destroyed the Golgi apparatus, which has great potential for the treatment of liver cancer.[57] Elhasany et al developed zein-CS NPs that integrate superparamagnetic iron oxide NPs for magnetic targeting and CS-mediated CD44 receptor targeting. This nanoplatform simultaneously encapsulated celastrol and sulfasalazine, demonstrating dual functionality for cancer theranostics through combined therapeutic intervention and diagnostic imaging capabilities.[58]

Precise spatiotemporal drug release from the carrier is crucial for the development of the delivery system. There is an urgent need for intelligent NPs that can achieve specific local delivery and respond to the tumor microenvironment. These NPs should be based on active targeting and environmental responsiveness, ensuring site-specific drug release and safety.[42] Environmentally responsive NPs, including pH, reactive oxygen species (ROS), redox and enzymatic triggers, can release drugs under specific conditions, which help to enhance the efficacy of targeted cancer therapy.[59,78–81]

Table 1 Application of CS-Based Polymeric Micelles in Tumor Therapy

Nanoplatforms	Tumor	Drug	Cell Line/Mouse	Results	Ref.
CS-DOCA	Breast cancer	DTX	MCF-7 cells	The NPs with higher degrees of DOCA substitution exhibit enhanced internalization and cytotoxicity	[54]
CS-DOX	Breast cancer	DOX and BBR	MCF-7 + MRC-5 co-cultured cell model/4T1 + NIH3T3 co-implanted mice model	The NPs inhibited the interaction of "CAFs-tumor cells" and significantly enhanced the therapeutic effect of breast cancer.	[15]
Zein-CS	Breast cancer	ATRA	Ehrlich Ascites tumor–bearing mice	The micelles exhibited enhanced internalization and synergistic cytotoxicity to breast cancer cells.	[55]
CS-His	Liver cancer	DOX	HepG2 cells	The NPs have higher toxicity to HepG2 cells compared to free DOX.	[56]
CS-DOCA	Liver cancer	RA and DOX	HSCs, HepG2 cells/fibrotic rat model	The NPs demonstrated hepatic-targeting capability, accumulated in HepG2 cells and destroyed the Golgi apparatus.	[57]
Zein-CS	Breast cancer	Celastrol	MCF-7, MDA-MB-231 cancer cells	The NPs combining magnetic targeting with the active targeting of CS result in higher cytotoxicity against MCF-7 and MDA-MB-231 cells.	[58]
CSA-TK-CHS	Breast cancer	DOX	4T1 and CT26 cells/4T1 tumor-bearing mice	The anti-tumor activity of the NPs was significantly higher than that of DOX·HCl in tumor-bearing Balb/c mice.	[59]
CS-anthocyanin	Colon cancer	DOX	HCT-116 tumor-bearing animals	The NPs causes nuclear contraction and cancer cell death, effectively inhibiting tumor growth.	[60]
CS-DTM-CTX	Breast cancer	Dasatinib	4T1 cells/ 4T1 tumor-bearing mice	The NPs reduced the size of the 4T1 tumor model and inhibited lung metastasis.	[61]
PLGA-ss-CSA	Lung cancer	DOX	A549 cells	The NPs have higher cytotoxicity in A549 cells compared to free DOX.	[62]
CSA-ss-TOS	Lung adenocarcinoma, gastric adenocarcinoma	DOX	A549, AGS cells /A549 tumor-bearing nude mice	The NPs have stronger antitumor activity than free DOX in A549-bring nude mice.	[63]
CS-DOCA	Melanoma	DTX	B16F10-bearing mice models	The NPs exhibit synergistic redox/enzymatic effects on tumor cells, enabling rapid drug release and producing potent anticancer activity.	[64]
CSA-DOCA	Breast cancer	DOX	4T1, MDA-MB-231 cells/4T1-bearing mice	The NPs exhibited the most potent effect on tumor growth and lung metastasis in orthotopic 4T1-bearing mice.	[65]

(*Continued*)

Table 1 (Continued).

Nanoplatforms	Tumor	Drug	Cell Line/Mouse	Results	Ref.
CSA-ss-deoxycholic acid	Triple-negative breast cancer	DOX	Triple-negative MDA-MB-231-bearing nude mice	The NPs with targeting CD44 and P-selectin receptors showed higher cytotoxicity and uptake in tumor cells than unmodified DOX micelles.	[66]
CS-Chol	Breast cancer	DOX	4T1, MCF-7, MDA-MB-231 breast cancer cells	The pH-sensitive NPs have a better therapeutic effect on breast cancer compared to free DOX	[4]
CS-b-PLGA	Breast cancer	DOX	MCF-7 cells/ Kunming mice	The micelle exhibits pH-dependent and sustained drug-release behavior, greatly prolonging the blood circulation time of DOX.	[67]
CS-His	Breast cancer	GOx and BSO	4T1 tumors in mice	The pH-sensitive NPs exhibit a good inhibitory effect on the growth of 4T1 tumors in mice.	[68]
CS-HS	Cholangiocarcinoma	DTX	QBC939 cells	The micelles rapidly release drugs at tumor pH, effectively killing cancer cells.	[69]
CSA-ss-Ce6	Triple-negative breast cancer	DOX	4T1, MDA-MB-231 cells/4T1-bearing Balb/c mice	Under laser irradiation, the NPs show enhanced antitumor efficacy.	[70]
CS-Rh-LA	Lung cancer	DTX	A549 cells	With the assistance of ultrasound, the NPs had a therapeutic effect on deep tumors	[71]
AC-CS-PpLX	Breast cancer	Apa and DOX	MCF-7 and MCF-7/ADR cells	The NPs successfully reversed tumor MDR through enhanced DOX sensitivity and ROS-mediated PDT.	[72]
CS-cys-QT/Ce6	Breast cancer	PTX	Multidrug-resistant MCF-7 cells	The NPs exhibit potent in vivo MDR inhibition and anti-metastatic efficacy through enhanced chemo-photodynamic therapy	[73]

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Thioketals (TK), diselenides, thioethers, aryl boronic esters and aminoacrylates are widely employed in the fabrication of ROS-responsive NPs. For example, Yu et al developed CSA-TK-CHS polymeric micelles by utilizing a ROS-cleavable TK linkage to conjugate CSA with cholesterol hemisuccinate (CHS). DOX encapsulated within these NPs demonstrated significantly enhanced release efficacy under elevated ROS levels. In vitro studies revealed that CSA-TK-CHS/DOX micelles exhibited markedly higher cytotoxicity in 4T1 and CT26 cells compared to free DOX. In vivo evaluations further demonstrated robust efficacy in suppressing tumor growth in 4T1 tumor-bearing mice.[59] Jeong et al prepared DOX-loaded CS-anthocyanin (ATC) nanocomplexes, which led to the fragmentation of the nanostructures in the presence of ROS. It was shown that CS-ATC-DOX significantly inhibited tumor growth due to the presence of ATC compared to CS-DOX.[60]

Dithiomaleimide (DTM) and disulfide bonds are used in the fabrication of redox-responsive NPs. Disulfide bonds are typically formed through the oxidation of two sulfhydryl groups without the involvement of a maleimide group. The synthesis of disulfide bonds is simplified, leading to their widespread use in the redox-responsive polymeric micelles.[82] Reduction-sensitive NPs utilizing disulfide bonds maintain stability during blood circulation, while enabling rapid degradation through sulfhydryl-disulfide exchange reactions within reducing microenvironments. This unique property has positioned them as a research hotspot for controlled drug release in tumor cells.[83] Tumors have a highly glutathione (GSH)-rich reducing environment, causing redox nanocarriers to decompose rapidly and enhance drug release. For example, Zhang et al used a chemical method to conjugate hydrophobic cabazitaxel (CTX) with CS through DTM, forming an amphiphilic redox-responsive nanosystem. After the dasatinib-loaded CS-DTM-CTX (CDC) was internalized by the tumor cells, the disulfide bonds were broken under the redox conditions of the tumor, accelerating the release of the drug. This disrupts the interaction between fibroblasts and cancer cells, effectively inhibiting tumor growth and metastasis.[61] Wang et al employed disulfide linkages to covalently couple hydrophobic poly (lactic-co-glycolic acid) (PLGA) with CSA, fabricating a redox-responsive CS-based nanosystem. PLGA-ss-CSA loaded with DOX was released more efficiently in the presence of GSH than in the absence of GSH. Therefore, the NPs were an effective carrier for inhibiting A549 cells.[62] Cai et al used disulfide bonds as linkages and designed redox micelles (CSA-ss-α-tocopherol succinate) for DOX delivery. Compared with non-responsive micelles, DOX-loaded responsive micelles had higher cytotoxic activity on A549 and AGS cells.[63] The redox-responsive nanocarriers have shown significant therapeutic advantages in tumor microenvironments with elevated GSH concentrations. Liu et al successfully encapsulated DTX into CS-ss-DOCA conjugate, developing dual redox/enzyme-responsive nanocarriers for the treatment of melanoma.[64] Yu et al designed CSA and AS1411 aptamer-mediated stimuli-responsive dual-targeting drug delivery systems (AS1411 aptamer-CSA-ss-DOCA) to suppress breast cancer metastasis.[65] Yu et al synthesized a targeted peptide (CDVEWVDVS)-modified CSA-ss-DOCA copolymer, which enabled DOX delivery for enhanced triple-negative breast cancer therapy.[66]

Ester and carbonate bonds are extensively utilized in the field of pH-responsive nanoparticle research. Their primary mechanisms of action involve serving as connecting links in carriers or forming specific chemical bonds in prodrugs, enabling pH-responsive release within the acidic microenvironment of tumors. Relevant studies have indicated that pH-dependent NPs also play a distinctive role in tumor therapy. Azimijou et al prepared CS-cholesterol nanoassemblies with carbonate ester bonds and tunable hydrophobic contents.[4] The characteristics of these bonds confer pH responsiveness of the CS-cholesterol NPs. Under acidic pH conditions, the conjugates rapidly decompose and release DOX for targeted drug delivery in the treatment of breast cancer. In vitro cytotoxicity assays demonstrated that DOX-loaded NPs had concentration-dependent anti-proliferative activity against 4T1, MCF-7 and MDA-MB-231 breast cancer cells. In comparison with free DOX, the NPs have been shown to enhance early apoptosis, improve cellular uptake, and better prevent tumor cell proliferation. Additionally, Zhang et al introduced weakly acidic carboxyl groups (-COOH) during the synthesis of CS-*b*-PLGA, endowing the resultant NPs with pH-responsive properties.[67]

It is crucial to consider both the characteristics of the linking moieties and the inherent properties of the chemical bonds. For example, the unique charge properties of histidine (His) lead to the disassembly of micelles under acidic conditions, enabling the pH-responsive behavior of CS-His NPs.[68] The CS-His micelles encapsulated with docetaxel (DTX) could effectively kill QBC939 cells and improve the therapeutic effects on cholangiocarcinoma.[69] The tumor microenvironment exhibits elevated intracellular GSH and acidic pH levels. The design of stimuli-responsive drug delivery systems capable of sensing acidic conditions to enhance drug release within tumor regions represents a critical

direction for future pharmaceutical research. This strategic approach holds significant potential for improving therapeutic precision while minimizing systemic toxicity through microenvironment-triggered activation mechanisms.

The intricate nature of the tumor milieu and the existence of multiple mechanisms necessitate the consideration of a multitude of factors in tumor therapy.[84] A single responsive mechanism or therapeutic modality remains challenging in achieving optimal therapeutic effects. Hence, integrating multiple strategies has been a key direction in the design of multi-responsive or multifunctional therapeutic systems. Yu et al have demonstrated that the integration of DOX into the CSA-ss-chlorin e6 (Ce6) delivery system enabled a combined chemo-photodynamic therapeutic strategy for triple-negative breast cancer, and significantly enhanced tumor suppression efficacy through synergistic effects.[70] Photodynamic therapy exhibited suboptimal therapeutic outcomes in the deep tumors due to the restricted penetration of laser light. Zhang et al developed the CS-Rh-LA graft by conjugating rhein (Rh) and lipoic acid (LA) to CS. DTX was effectively encapsulated into CS-Rh-LA nanoplatform, resulting in the tumor-specific drug release and structural stability during systemic circulation. This experimental evidence indicated the potential of Rh in synergizing with chemotherapeutic agents under ultrasound irradiation for sonodynamic therapy (SDT) against lung cancer (Figure 1).[71]

Conventional chemotherapeutic agents lack specificity for cancer cells and thus have toxic effects on normal cells. The development of drug resistance in tumor cells during treatment is a major challenge. A drug efflux process facilitated by P-glycoprotein on the cell membrane, which induces drug resistance in tumor cells, is a key factor that needs to be addressed. NPs with P-glycoprotein inhibitors, such as apatinib (Apa) and quercetin (QT), is regarded as an effective strategy to overcome tumor resistance.[85,86] Wei et al utilized the hydrophobic interactions to co-encapsulate Apa and DOX into amphiphilic acetylated-CS-PpLX (ACP) micelles. The ACP-DOX+Apa micelles generate ROS upon laser irradiation, leading to the disintegration of micelles. Apa has been released to inhibit P-glycoprotein, thereby increasing DOX accumulation in MCF-7/ADR cells. Concurrently, the ROS from photodynamic therapy (PDT) triggered mitochondria-dependent apoptosis, enhancing the synergistic effects between Apa-induced DOX sensitivity and ROS-mediated PDT.[72] Shi et al reported that PTX was encapsulated into CS-cys-QT/Ce6. With the help of QT, the anticancer efficiency of PTX against multidrug-resistant MCF-7 cells was enhanced. Under the laser irradiation, ROS was produced to promote the apoptosis of the cells.[73] Therefore, the combination therapy of chemotherapy-PDT is expected to become an effective way to overcome tumor resistance and improve the antitumor efficacy.

Nanogels

Nanogels exhibit various properties of NPs and hydrogels.[87,88] Nanogel is a three-dimensional structure that is cross-linked by physical or chemical means.[89] However, the main difference between nanogels and hydrogels is their size.[90] The minute size

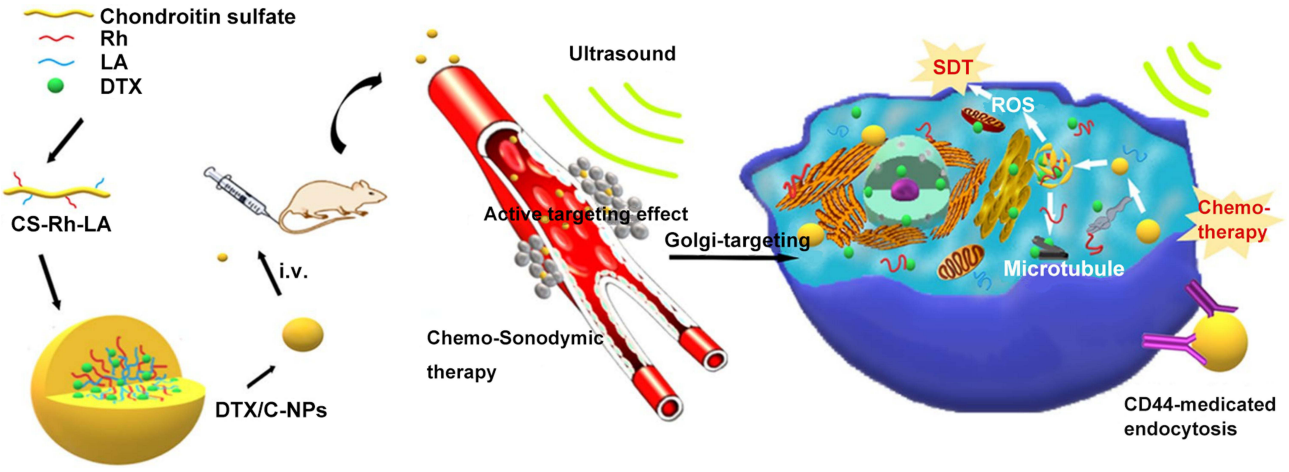

Figure 1 The synthesis of DTX/C-NPs and intravenous injection into mice through the synergistic effect of chemo-sonodynamic therapy to achieve the treatment of lung cancer. Adapted from Zhang Y, Khan AR, Yang X, et al. A sonosensitiser-based polymeric nanoplatform for chemo-sonodynamic combination therapy of lung cancer. J Nanobiotechnol. 2021;19:57. http://creativecommons.org/licenses/by/4.0/.[71]

of nanogels facilitates effective penetration through biological barriers.[87,91] Nanogels exhibit exceptional versatility in drug delivery, capable of encapsulating both hydrophilic and hydrophobic therapeutic agents. Their three-dimensional network structure acts as a protective matrix, shielding loaded drugs from aggregation, denaturation and enzymatic degradation. Notably, the soft and deformable architecture of nanogels enables efficient transport through intercellular gaps or uptake via cellular endocytosis.[92–94] This unique property overcomes physiological barriers such as the extracellular matrix and epithelial tight junctions, facilitating enhanced tissue penetration and intracellular delivery. Moreover, their gel-like consistency enables adaptive deformation under mechanical stress, allowing passage through narrow capillaries and improving targeting efficiency to pathological sites. Nevertheless, studies on CS-based nanogels remain relatively limited in the antitumor applications.

Campea et al encapsulated SNP-CHO NPs within disulfide-crosslinked CS-based nanogels. In vitro studies revealed that the DOX-loaded CS-SH@SNP-CHO nanogels could release the drug with accelerated kinetics in a highly disulfide-reducing environment. In vivo experiments showed that the small-sized drug-loaded SNPs allowed for deeper drug penetration into poorly vascularized tumor cores compared to free DOX. With increasing concentrations of loaded DOX, the nanoassembly exhibits better CT26 cancer cell toxicity than SNP-CHO NPs. The nano-assemblies exhibited lower nonspecific tumor toxicity and greater therapeutic potential for treating larger tumors while avoiding the mild cardiac tissue toxicity associated with free DOX (Figure 2).[95] Setayesh et al showed that CS-octadecylamine conjugates could self-assembly to deliver curcumin and be effectively taken up by MCF-7 cancer cells.[96] Therefore, these nanogels hold promise for the effective inhibition of cancer cells.

The use of nanogels in combination with other components or therapeutic approaches, especially encapsulated in hydrogels, has been an effective strategy. Gil et al investigated an injectable hydrogel incorporating CS-nanogels loaded with cisplatin. The nanogels were synthesized through a metal-chelator coordination crosslinking method and subsequently integrated into a pH/temperature-dual responsive polyethylene glycol-poly (amino ester urethane) hydrogel matrix to accomplish tumor-targeted cisplatin delivery.[97] This structure involved the combination of a small molecule drug with an organic polymer material to achieve a specific drug delivery and therapeutic effect. Through this combination, the stability of the drug can be enhanced. The release rate can be controlled, and the interactions with specific cell types have been strengthened.

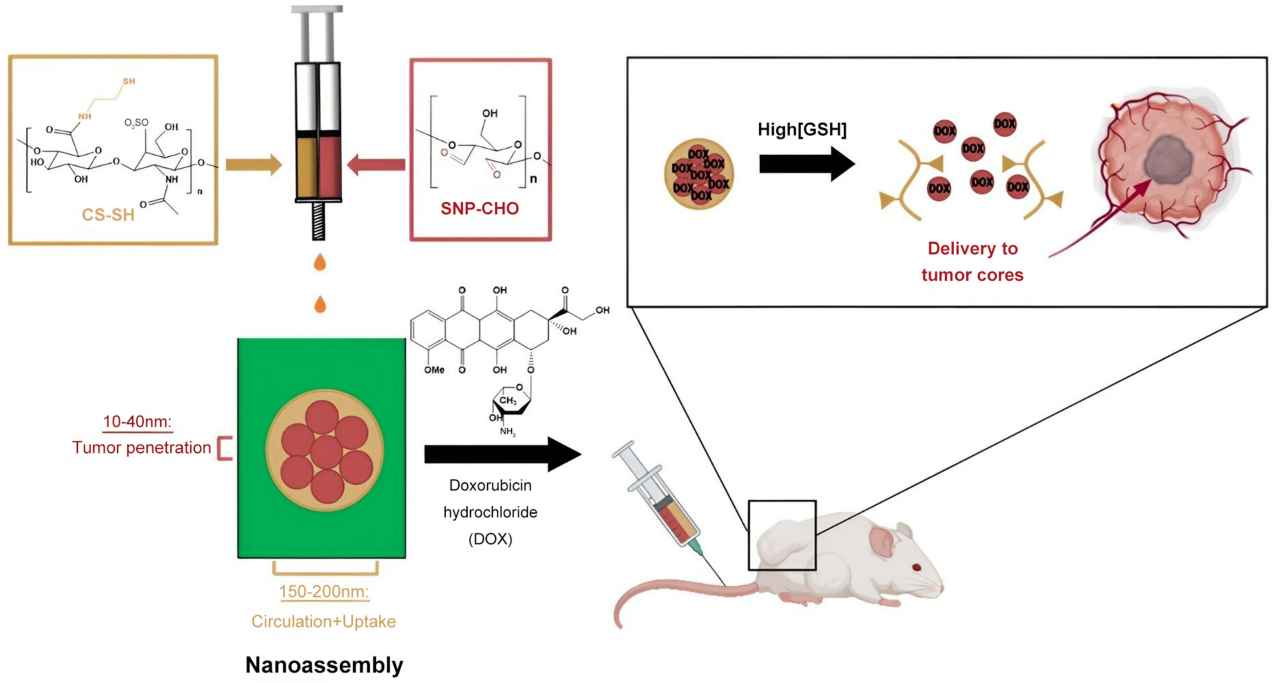

Figure 2 SNP-CHO NPs are encapsulated in disulfide-bonded cross-linked CS-based nanogels for chemotherapeutic drug delivery. Adapted with permission from Campea MA, Lofts A, Xu F, et al. Disulfide-cross-linked nanogel-based nanoassemblies for chemotherapeutic drug delivery. ACS Appl Mater Interfaces. 2023;15:25324–25338. Copyright 2023 American Chemical Society.[95]
Abbreviations: CS-SH, disulfide-crosslinked thiolated chondroitin sulfate-based nanogels; SNP, Starch NPs; SNP-CHO, acterization of aldehyde-functionalized SNPs. Adapted from previous report (Reference 95).

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CS-Conjugated Drug NPs

Polymer-conjugated drug NPs are macromolecular structures in which the polymer is covalently bound to one or more therapeutic agents with pharmacological activity.[98] CS-drug NPs exhibited distinctive physicochemical properties and tumor-targeting capabilities. Unlike traditional physical encapsulation methods, CS-drug conjugates emphasize the direct chemical bonding of drugs to CS. These NPs achieve drug loading through covalent coupling, forming stable molecular conjugates rather than relying on physical entrapment within a carrier matrix. This type of nanoparticle also exhibits spontaneous self-assembly, producing amphiphilic polymers with hydrophobic drugs on the inside and hydrophilic CS on the outside. The structure of the NPs is more stable due to the involvement of chemical bonds. Compared to the simple encapsulation of drugs into the nanocarriers, the polymer-drug conjugates significantly enhanced drug loading capacity via covalent conjugation chemistry.[99] Xie et al reported that CSA-DOX NPs showed a significant increase uptake in A549 cells compared to free DOX. Further, the NPs can be a potential therapeutic platform for the lung cancer treatment.[29] Liu et al described that the CS-DOX-PLGA obtained after modifying CS-DOX with PLGA was more accessible to A549 cells. The NPs demonstrated reduced cardiotoxicity and maintained comparable antitumor efficacy through enhanced tumor-targeted drug delivery.[100] Liu et al designed the CS-ADH-Ce6-LA to produce potent therapeutic and anti-metastatic effects on melanoma in a combined chemo-acoustic kinetic manner.[101] Li et al conjugated the photosensitizer Ce6 and RA to CS, thereby delivering two therapeutic agents. The Ce6-CS-RA NPs induced Golgi apparatus disruption and enhanced PDT efficacy against melanoma (Figure 3).[102] Wang et al reported the development of self-assembled micelles derived from a chondroitin sulfate-cinnamaldehyde-curcumin-triphenylphosphine (CS-CA-CUR-TPP, abbreviated as CCCT) conjugate. The CCCT NPs were efficiently enriched and internalized by A549 cancer cells. Moreover, CCCT effectively inhibited tumor growth and helped overcome apoptosis resistance in cancer therapy.[103]

It also has intelligent stimulus-responsive drug release mediated by pH-cleavable bonds and GSH-sensitive disulfide bonds.[104] This nanoplatform has been shown to enhance the therapeutic efficiency of the administered drug while reducing its distribution within normal tissues. Onishi et al investigated the potential of a novel nanomedicine, a combination of DOX and adipic acid dihydrazide-CS (CS-ACH), to enhance the efficacy of the drug under acidic conditions. In vitro experiments showed that CS-ACH-DOX resulted in accelerated drug release under acidic conditions. However, the therapeutic effect was not as pronounced as that of the free drug. In vivo experiments demonstrated that CS-ACH-DOX exhibited enhanced efficacy in the acidic tumor environment compared with free DOX. These results inferred that the nanodrug carrier has the potential to serve as a promising therapeutic agent.[43] Hu et al developed CS-based NPs, designated as the CS-ss-IR806 conjugate, for prostate cancer (PCa) therapy. The incorporation of disulfide bonds within the polymeric NPs conferred redox-responsive properties. In the presence of the photosensitizer IR806, the NPs demonstrated synergistic capabilities with SDT and PDT, thereby achieving superior therapeutic efficacy against localized PCa.[105] Li et al reported that Cys-DTX was encapsulated into CS-ss-DTX NPs, and Cys-DTX/CS-ss-DTX NPs were formed by self-assembly. These NPs exhibited redox-responsive release of DTX as well as high permeability and cytotoxicity in tumor tissues.[106] As previously reported, CS was conjugated with dasatinib (DAS) via the cathepsin B responsive GFLG peptide linker to form CS-GFLG-DAS (CGD). The resulting CGD NPs were capable of reversing the phenotype of cancer-associated fibroblasts and modulating extracellular matrix biosynthesis, thereby enhancing the therapeutic efficacy of anti-PD-1 treatment in 4T1 tumor-bearing mice.[107] Notably, Poursani et al developed esterase-responsive CS-chlorambucil (Chl) prodrugs and redox-responsive CS-LA conjugates, which were fabricated into enzyme- and redox-responsive NPs via a water/solvent evaporation technique. Subsequently, DOX was encapsulated within these NPs, constituting the first stimuli-responsive NPs. These NPs demonstrated triggered release of Chl and DOX into MDA-MB-231 cells in response to specific biochemical stimuli. The dual-responsive co-release system for multiple anticancer drugs synergistically enhanced cellular internalization and markedly improved antitumor efficacy.[80] This approach significantly improved the efficacy compared to the NPs co-loaded with a single drug and a single responsive modality. Consequently, these NPs were anticipated to serve as a highly effective treatment for aggressive solid cancers, particularly triple-negative breast cancer. Therefore, CS-conjugated prodrug NPs had a high drug-loading capacity and microenvironment-responsiveness at the tumor site.

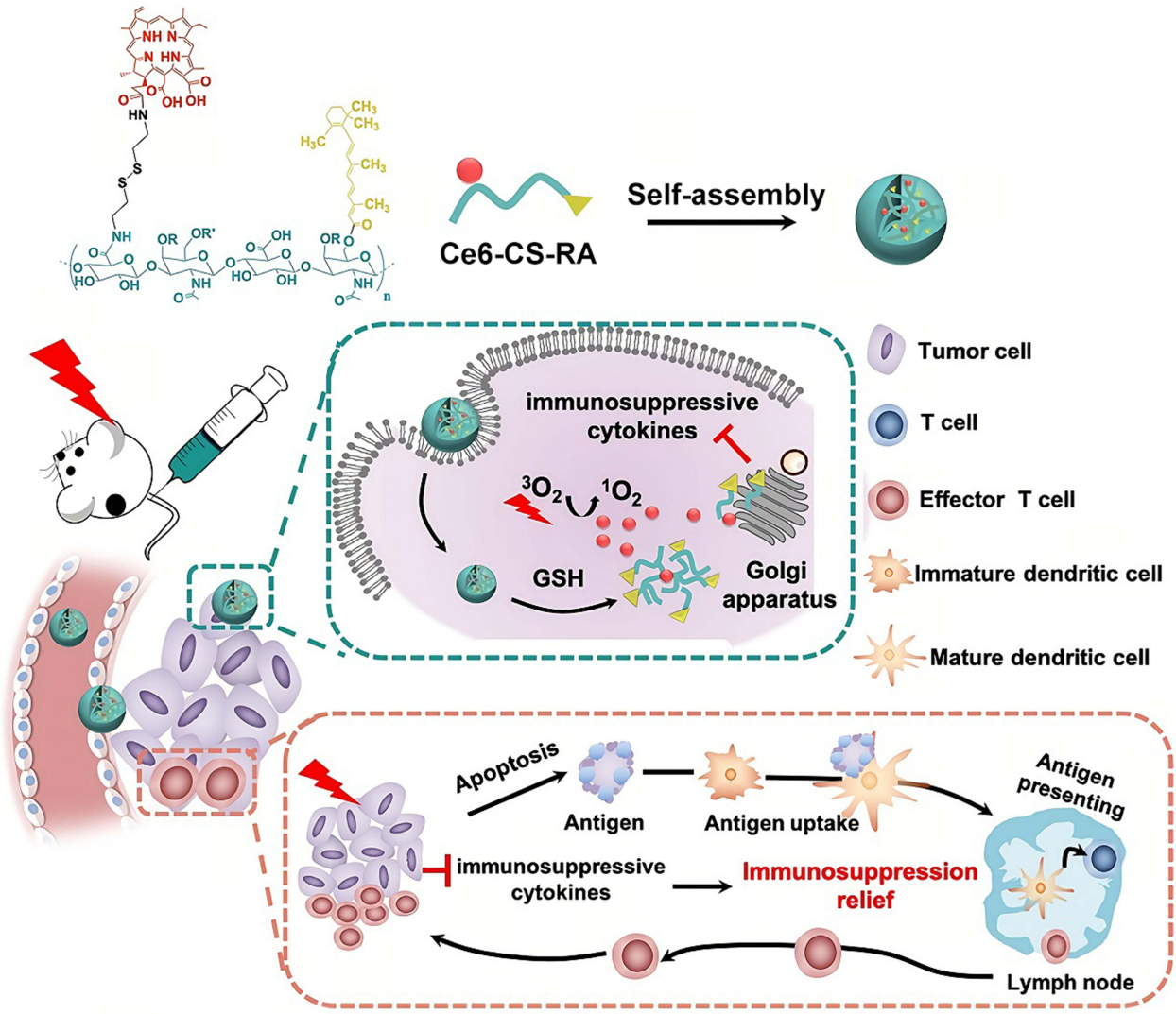

Figure 3 Golgi apparatus-targeted prodrug Ce6-CS-RA NPs in vivo application for enhanced photodynamic immunotherapy. Reprinted from Acta Biomaterialia, 146, Haohuan Li, Caifeng Deng, Yulu Tan, Jianxia Dong, Yuanhao Zhao, Xiaorong Wang, Xingyue Yang, Jingwen Luo, Huile Gao, Yuan Huang, Zhi-Rong Zhang, Tao Gong, Chondroitin sulfate-based prodrug nanoparticles enhance photodynamic immunotherapy via Golgi apparatus targeting, 357-369, Copyright 2022, with permission from Elsevier.[102]
Abbreviations: Ce6, chlorin e6; RA, retinoic acid. Adapted from previous report (Reference 102).

CS-Coated NPs

CS is not only used as a synthetic drug carrier but also as an excipient for the coating of other carriers.[14] Lipid nanoparticles (LNPs) have emerged as drug delivery vehicles in contemporary pharmaceutical research, particularly for lipophilic therapeutic agents such as paclitaxel, vincristine, and DTX.[108,109] However, the clinical translation of these nanocarriers faces critical barriers including low encapsulation efficiency for small molecule drugs, cytotoxicity induced by cationic lipids, and systemic toxicity resulting from liver penetration.[110–112] These issues not only affect the drug-loading capacity of NPs but also limit their safety and efficacy in vivo. CS and its derivatives have been demonstrated to protect NPs from premature clearance during circulation. CS-coated NPs achieve prolonged circulation via steric stabilization and facilitate efficient intracellular drug delivery, while the NPs could achieve ligand-receptor binding specificity by active targeting.[113,114] Therefore, CS coating emerges as a viable strategy to mitigate cationophore toxicity. By integrating steric stabilization, active targeting and toxicity mitigation, CS-coated NPs offer a multifunctional platform for advanced drug delivery. For example, Liang et al employed the CS derivative (CS-oleic acid) to encapsulate DOX nanocrystals. This approach showed the drug targeting and responsiveness to the internal environment of the tumor.[44] It also exhibited superior therapeutic effects compared

to the DOX nanocrystals coated with the PEG-PCL. LNPs coated with CS and its derivatives exhibited significantly prolonged retention at various mucosal sites, thereby markedly improving the bioavailability of the loaded drugs.[34]

The surface coating of NPs with CS mainly takes the following forms: (1) Layer-by-layer packaging of NPs by the positive and negative charge properties to minimize the adverse drug damage; (2) Formation of amide-bonded crosslinked CS shells by using its free radicals to encapsulate NPs. Zhang et al synthesized the NPs (TPP-PEG-ss-PLA) by grafting triphenylphosphine (TPP) onto poly (ethylene glycol) (PEG)-poly (D, L-propylene lactone) (PLA) copolymer.[31] The surface of the NPs has a positive charge. The negative charge of CS is attracted to the positive charge of the NPs to form CS-coated NPs (CS/TPP-PEG-PLA@DOX). The final product is a multifunctional nanosystem with dual targeting of cell membranes and mitochondria, as well as dual responsiveness to pH and redox conditions. In vivo tests exhibited that this innovative therapeutic approach had considerable promise for the treatment of hepatocellular carcinoma. Abdelaziz et al prepared anionic LNPs by embedding positively charged pemetrexed-resveratrol-liquid crystalline NPs (PEM-RES-LCNP) into a negatively charged CS shell and then repeated with positively charged lactoferrin (LF). This layer-by-layer targeted modification prepares inhalable NPs that can significantly improve the therapeutic effects on lung cancer while minimizing damage to normal cells.[32] Abd Elwakil et al employed negatively charged CS and positive LF to achieve layer-by-layer encapsulation of DOX and ellagic acid nanocrystals. The resulting NPs were coated for inhalation use in the treatment of lung cancer.[115] Aly et al enclosed pterostilbene-loaded solid lipid nanoparticles (SLNs) with negatively charged CS and subsequently with positively charged LF. These dual-targeted NPs demonstrated remarkable antitumor efficacy in breast cancer models.[116] Ren et al developed a pH- and glutathione-dual-responsive drug delivery system by using maleiminated polyethylene glycol and polylactide block copolymer as the core material. DOX was encapsulated within the nanoparticle, while thiocollagenase and maleimide were conjugated to the nanoparticle surface. To enhance stability and targeting, the NPs were further coated with CS as a protective layer. This design enabled the NPs to actively target CD44 receptors on cancer cells, resulting in enhanced anticancer efficacy in breast cancer-bearing mice.[117]

Luo et al used cationic liposomes consisting of soybean phosphatidylcholine, cholesterol and the positively charged lipid 1,2-dioleoyl-3-trimethylammonium propane to encapsulate the albumin-bound PTX complex (BSA-PTX). TPGS, a P-gp inhibitor, was then immobilized on its surface. Negatively charged CS was coated on its positively charged surface. The shell of CS can respond to the intra-tumor environment and accelerate the release of drugs for the effective treatment of drug-resistant breast cancer.[118] Kim et al encapsulated cationic solid lipid NPs containing DTX with negatively charged glycoconjugate-CS conjugates. This orally administered drug demonstrated the capacity to maintain blood levels for 24 hours and exhibited potent anticancer efficacy, completely inhibiting tumor formation.[119] Du et al used a method of physical encapsulation to improve the efficacy of NPs. The NPs were encapsulated by amide-bonded cross-linked CS shells (DOX@MOF-COD@CS). As the CS-encapsulated NPs reach the high-GSH intra-tumoral environment, the CS shell layer with disulfide bonds was disintegrated.[120] Furthermore, the nano-enzymes and natural enzymes initiated a cascade catalysis, which led to the conversion of cholesterol into hydroxyl radicals, providing a new idea for breast cancer cells to reverse drug resistance.[120] This approach diverges from charge-mediated encapsulation strategies, employing physical entrapment rather than electrostatic interactions for nanoparticle stabilization.

CS-Modified NPs

The presence of reactive groups of CS makes it highly suitable for the surface chemical modification of NPs. CS-modified and CS-coated NPs offer the primary goal of enhancing nanocarrier stability. However, their mechanisms of action exhibit distinct differences. CS-coated NPs achieve surface encapsulation through physical adsorption, whereas CS-modified NPs rely on covalent bond formation between reactive groups in CS molecules and functional groups on the NP surface. This covalent bonding strategy in CS-modified NPs circumvents desorption issues inherent to physical encapsulation, thereby conferring superior stability.[121] Additionally, CS-modified NPs enable functional group integration, such as pH-responsive moieties for environment-sensitive drug release.[77] The covalent linkage ensures long-term stability in biological fluids, making CS-modified NPs particularly suitable for applications requiring prolonged circulation or site-specific drug delivery. Zhang et al prepared liposomal NPs chemically surfaced with CS from amphiphilic CS polymers for co-delivery of DOX and retinoic acid. The functionalized modification not only maintained the original drug loading capacity but also promoted the uptake of the particles by B16F10 and 4T1 cells, leading to the enhanced

efficacy of the drug.[122] Zu et al constructed the PLGA-based camptothecin (CPT)-loaded polymeric NPs with the surface modification by CS or carboxymethyl cellulose. The targeted CS-modified NPs with CPT encapsulation have demonstrated superior therapeutic outcomes compared to those with the surface of carboxymethyl cellulose.[123]

CS binds to LNPs by chemical modification of their surfaces. Luo et al utilized the CS-modified dual drug-loading LNPs to deliver RA and DOX, intending to disrupt the Golgi apparatus and DNA to treat hepatocellular carcinoma. In vivo results demonstrated that DOX+RA-CSNs exhibited superior anti-cancer efficacy and effectively impeded tumor growth compared to LNPs devoid of CS modification (Figure 4).[124] Liu et al employed disulfide bonds to graft CS onto the surface of mesoporous silica NPs loaded with PTX and quercetin (QT). Surface modification of CS significantly improved the nanoparticle's internalization kinetics. The residence time of the drug at the tumor site was prolonged, and tumor resistance was reversed.[125] Yu et al prepared photosensitizer indocyanine green (ICG)-loaded amorphous calcium-carbonate (ICG@) nanoparticle. Both ICG@ and DOX were encapsulated into PLGA-ss-CSA (PSC) nanoparticles. The resulting PSC/ICG@+DOX NPs exhibited pH- and reduction-responsive drug release, effective CD44 targeting and chemo-photothermal cancer therapy (Figure 5).[77]

Dendritic polymers are radially branched architectures and precisely controlled topological organization.[126,127] Due to their progressively controllable synthesis process, dendrimers combine the properties of both polymers and molecular chemistry. The inner cavity and peripheral functional groups of these polymers can be used to encapsulate bioactive molecules or chemically bond with bioactive molecules. The surface of dendrimer polymers could be modified with CS

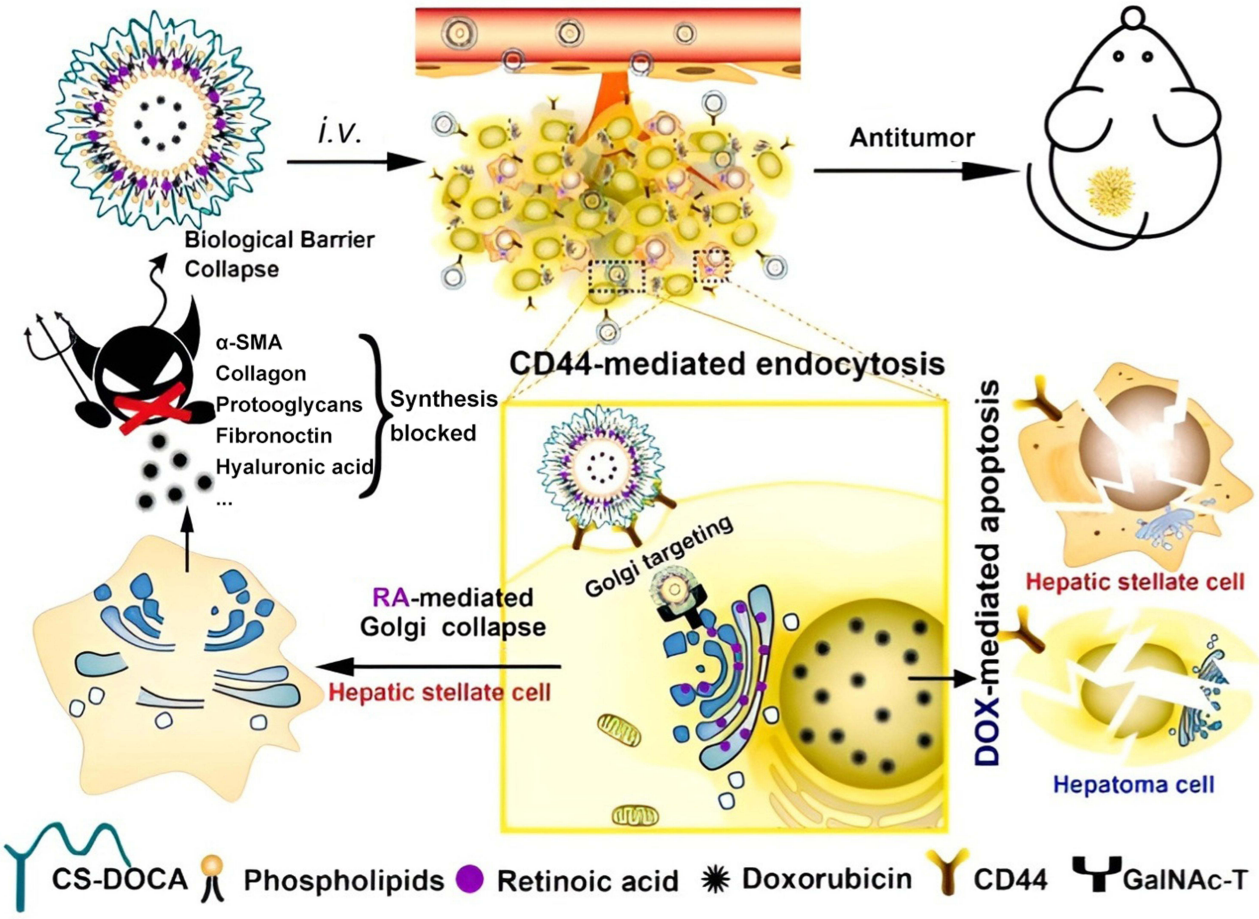

Figure 4 DOX+RA-CSNs target liver cancer cells via CD44-mediated endocytosis, then target Golgi apparatus via interaction with GalNAc-T. Reprinted from Carbohydrate Polymers, 249, Jingwen Luo, Tao Gong, Lixin Ma, Chondroitin-modified lipid nanoparticles target the Golgi to degrade extracellular matrix for liver cancer management, 116887, Copyright 2020, with permission from Elsevier.[124]

Abbreviations: DOCA, deoxycholic acid; i.v., intravenous injection; GalNAc-T, Golgi apparatus via interaction with N-acetylgalactosaminyltransferases.

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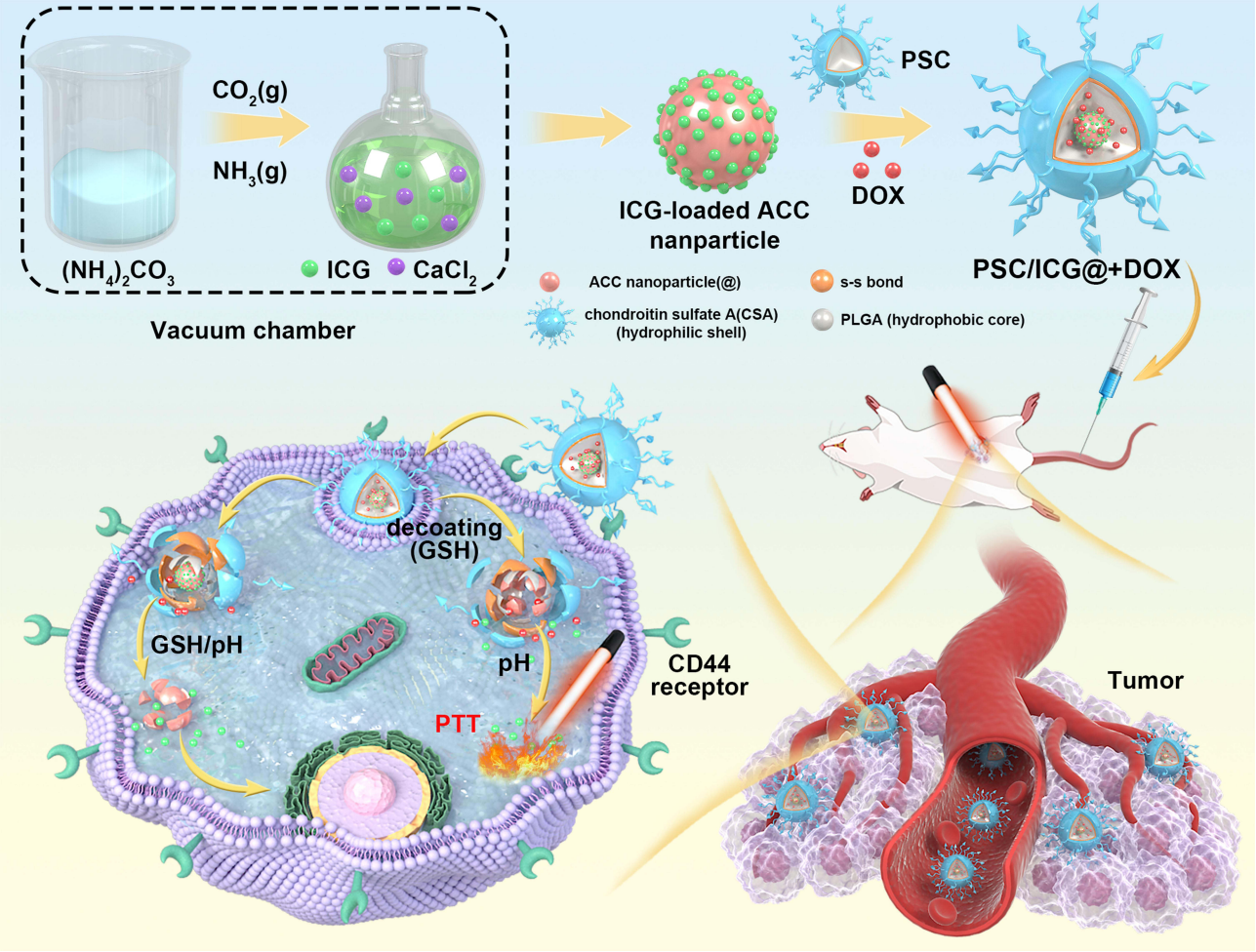

Figure 5 PSC/ICG@+DOX exhibits pH and redox dual responses. Under laser irradiation, the synergistic treatment of chemotherapy and photothermal therapy has shown significant anti-cancer efficacy in 4T1-bearing mice. Reproduced with permission from Yu J, Wang L, Xie X, et al. Multifunctional nanoparticles codelivering doxorubicin and amorphous calcium carbonate preloaded with indocyanine green for enhanced chemo-photothermal cancer therapy. Int J Nanomed. 2023;18:323–337.[77]
Abbreviations: PSC, poly (lactic acid-hydroxyacetic acid copolymer)-ss-CSA; ICG, indocyanine green. Adapted from previous report (Reference 77).

to target CD44 receptor. The potential of polyamidoamine (PAMAM) dendrimers for biomedical applications has been further enhanced by the modification with CS. Chen et al coupled CS with PAMAM via the Michael reaction to obtain the CS-PAMAM.[128] The polymeric nanoparticles were mixed with miR-34a, resulting in the formation of NPs containing miR-34a (CS-PAMAM/miR-34a). In vitro experiments indicated that the presence of CS as a targeting ligand further enhanced the transfection efficiency of miR-34a. CS-PAMAM/miR-34a demonstrated significant inhibition of lung adenocarcinoma growth in vivo and the ability to induce tumor cell apoptosis. Duan et al constructed the CS-PAMAM nanosystem for miR-34a delivery and used the human pancreatic cancer cell line MiaPaCa-2 as a model. Under the action of miR-34a, the NPs activated apoptosis and cell cycle arrest in pancreatic cancer cells, leading to significant suppression of cell proliferation and inhibition of cancer cell migration.[129]

CS-Based Nanoplatform in Other Diseases Therapy

CS-based nanoplatforms play an important role in tumor therapy. Meanwhile, their applications have been extended to a variety of diseases such as ophthalmology, liver, and neurodegenerative diseases. In particular, CS exhibits significant anti-inflammatory activity, enhancing the bioavailability and targeting of nanoplatforms. This provides a highly effective strategy for the treatment of inflammation-related diseases.

Ophthalmic Diseases

Dry eye has a significant impact on the quality of life of patients, especially among an aging population.[130,131] CS with the targeting and adhesion properties may play a beneficial role in the treatment of dry eye. Zhu et al developed dexamethasone (DEX)-loaded CS-cysteine-functionalized cationic nanostructured lipid carriers (DEX-CS-Cys-cNLCs) through surface modification of cNLCs. The approach involved a coupling of CS and L-cysteine (CS-Cys) to create an ocular delivery system. The nanostructured carrier demonstrated stronger retention and duration of action. In addition, these NPs relieved dry eye symptoms, effectively repaired corneal damage and improved tear film stability.[132] Tan et al reported the surface modification of DEX-loaded NLCs with (3-aminomethylphenyl)boronic acid-conjugated CS (APBA-CS). Compared with conventional ocular solutions, APBA has been shown to extend the retention time of the pharmaceutical agents within the cornea. APBA-CS exhibited strong mucoadhesive properties and therapeutic benefits for dry eye syndrome.[133] Abdullah et al found that CS-chitosan NPs facilitated the delivery of bromfenac sodium, leading to significantly high transcorneal permeation and corneal retention of bromfenac through the NPs. The NPs could be a potential vehicle for ocular drug delivery.[134] Corneal reinforcement is also of significance in the treatment of infectious corneal diseases, including conical corneas, corneal ulcers, and keratitis. Wang et al chemically modified CS with *N*-hydroxy succinimide (NHS) to obtain CS-NHS. The CS-NHS conjugate cross-linked with collagen and proteoglycans in the cornea, which could decrease the rate of dissolution and increase Young's modulus, the diameter and the density of collagen fibers. Reduced expression of pro-inflammatory genes was also observed, while the cornea was strengthened. This method of corneal reinforcement is straightforward and efficacious.[135]

Available commercial drugs for dry eye disease (DED) are predominantly focused on symptomatic treatment. CS-based nanoplatforms also follow this therapeutic principle. In the treatment of ophthalmic diseases, these nanoplatforms rely on enhanced permeability and mucosal adhesion for therapeutic purposes. This long-term action is particularly effective in relieving dry eye. Notably, CS-based nanocarriers could shift from symptom alleviation to targeting the underlying pathological mechanisms, thereby providing a novel therapeutic approach for DED.

Liver Diseases

Liver fibrosis is a critical stage in the progression of liver diseases towards cirrhosis, and existing pharmacotherapies have limited ability to halt or reverse this pathological progression.[136] CS-based NPs as an emerging therapeutic agent, have shown unique potential and advantages in reversing liver fibrosis. Zhang et al successfully prepared CS-modified lipid NPs by using phosphatidylcholine (PC), cholesterol, CS-PEG-DSPE, and PEG-DSPE. Subsequently, Vismodegib (VDG) was encapsulated into these NPs, resulting in formation of CS-NPs/VDG. It was found that CS-NP/VDG could effectively restore the pore structure of liver sinusoidal endothelial cells (LSECs) and inhibit the activation of hepatic stellate cells (HSCs). As previously described, CS was conjugated with 1-hexadecylamine (HDA) via an amide bond to yield the amphiphilic CS-HDA. The imatinib-encapsulated nanoparticles (IM-CS NPs) exhibited enhanced targeting efficiency toward activated HSCs and effectively suppressed HSC overactivation by modulating the PDGF and TGF-β signaling pathways.[137] Zhang et al reported that CS-modified, vismodegib-loaded nanoparticles (CS-NPs/VDG) effectively normalized the fenestrae phenotype of liver sinusoidal endothelial cells and restored HSCs to a quiescent state by inhibiting the Hedgehog signaling pathway.[138] Luo et al demonstrated that CS coated multilayered NPs encapsulating collagenase and silibinin (COL + SLB-MLPs) degraded the dense collagen stroma, while silibinin inhibited activated hepatic stellate cells. COL + SLB-MLPs were delivered to the cirrhotic liver, leading to the fact that silibinin and collagenase synergistically inhibited fibrosis in mice.[139] Cirrhosis represents a subsequent stage in the progression of liver fibrosis. Tan et al developed a novel modified nanoplatform (SRF-CS-PSA NPs) in which sorafenib (SRF) was loaded by palmitic acid-modified albumin (PSA) and further functionalized with CS. The resultant SRF-CS-PSA NPs exhibited dual targeting capabilities and inhibitory effects on HSCs and macrophages, which effectively reversed the process of cirrhosis.[140] Li et al constructed a multifunctional nanoparticle CREKA–CS–RA (CCR) based on CREKA (a specific ligand of fibronectin), CS (CD44 targeting ligand) and retinoic acid (RA, a Golgi apparatus-disturbing agent). Vismodegib-loaded CCR NPs disrupted the structure and function of Golgi apparatus, and inhibited the hedgehog signaling pathway, thus significantly suppressing hepatic stellate cells activation and extracellular matrix secretion.[141]

Neurodegenerative Diseases

Neurodegenerative diseases, particularly Alzheimer's and Parkinson's diseases, are becoming increasingly prevalent.[142,143] CS-based nanoplatforms showed great promise in the treatment of Alzheimer's disease (AD). Tian et al developed a CS-modified MoS_2 nanoenzyme (CS@MoS_2) and evaluated its potential in anti-AD research. CS@MoS_2 demonstrated a substantial inhibitory effect on $A\beta_{1-40}$ aggregation and prevented toxic injury in SH-SY5Y cells, protecting cells from oxidative stress by modulating ROS and superoxide dismutase (SOD) activities. Furthermore, CS@MoS_2 facilitated a balanced intracellular Ca^{2+} level and down-regulated Tau phosphorylation via GSK-3β. In addition, CS@MoS_2 inhibited MAPK phosphorylation and the translocation of p-NF-κB (p65). These effects of CS@MoS_2 effectively improved learning, memory, and anxiety in D-gal/$AlCl_3$-induced AD mice.[144]

Ji et al reported that CS nano-selenium CS@Se alleviated anxiety, enhanced learning and memory, reduced cellular edema and abscesses, protected mitochondria, and improved hippocampal neuronal synaptic structure in AD mice. In addition, CS@Se increased SOD, glutathione peroxidase (GSH-Px), Na^+/K^+-ATPase and choline acetyltransferase levels, and decreased malondialdehyde and acetylcholinesterase levels. CS@Se regulated GSK-3β expression, attenuated Tau protein hyperphosphorylation, activated extracellular signal-regulated kinase 1/2, and p38 mitogen-activated protein kinase signaling pathways, inhibited nuclear transcription factor kappa B (NF-κB) nuclear translocation, and regulated pro-inflammatory cytokine expression. These effects delayed the development of AD and enhanced cognitive performance in mice.[145] Gao et al ascertained that CS@Se effectively inhibited the aggregation of β-amyloid (Aβ), reduced damage to the cytoskeleton, attenuated oxidative stress and the hyperphosphorylation of Tau protein.[146] Hence, CS@Se had the potential as a potential multifunctional drug for the treatment of AD. Feng et al constructed a transmembrane peptide-CS-gold nanoparticle (TAT-CS@Au) nanoparticle, which exhibited favorable cellular uptake and transport ability, and effectively inhibited $A\beta_{1-40}$ accumulation and reduced apoptosis, thereby alleviating oxidative stress and cholinergic damage by regulating the levels of ROS, malondialdehyde, GSH-Px and acetylcholine. Furthermore, TAT-CS@Au nanoparticle could inhibit Tau phosphorylation, NF-κB nuclear translocation, and the production of inflammatory factors, thus providing a novel and promising approach to anti-AD therapy.[147]

The treatment of AD poses significant challenges. Previous therapeutic interventions have predominantly concentrated on alleviating symptoms. Specifically, CS-based nanoplatforms focused on the underlying mechanisms that facilitate disease progression, which could lead to a potential treatment for AD.

Inflammation

CS possesses inherent anti-inflammatory properties. However, its therapeutic efficacy via oral administration has been limited due to poor bioavailability. To overcome this challenge, researchers developed a CS-based nanoscale delivery system. This platform enabled the controlled release of anti-inflammatory agents while simultaneously generating bioactive CS fragments from the nanocarrier itself. This dual-action mechanism synergistically enhanced the anti-inflammatory effect by combining pharmacological intervention with the intrinsic therapeutic activity of the carrier material. In recent years, CS-based nanoplatforms have demonstrated significant potential in the treatment of inflammatory diseases, such as ulcerative colitis (UC), rheumatoid arthritis, osteoarthritis, and periodontitis.[148–151]

As previously described, rosmarinic acid-CSA nanoconjugate was synthesized. The drug-conjugated nanoassemblies significantly attenuated colonic inflammation compared to free rosmarinic acid in dextran sulfate sodium-induced acute colitis mouse model.[48] Deng et al developed licofelone-loaded NPs (LCF-CSBN) composed of CS and bilirubin. These NPs effectively alleviated joint inflammation, oxidative stress and cartilage degeneration in osteoarthritis model rats.[152] As previously studied, intra-articular nanohybrids were developed for the co-delivery of CS, glucosamine sulfate and gold, aiming to achieve synergistic anti-inflammatory and cartilage regenerative effects.[153] Dubashynskaya et al used CS and diethylaminoethyl chitosan (DeaeCS) to prepare dexamethasone phosphate (DexP)-loaded NPs (Dexp-CHS-DeaeCS -Zn). The study found that Zn^{2+}-containing NPs exhibited relatively small dimensions. This phenomenon resulted in the sustained release of DexP from the NPs. The combination of the NPs' mucosal adhesion and prolonged drug release contributed to a favorable anti-inflammatory effect. The alteration of the ratio of anionic and cationic polymers, with consideration for the charged nature of the bound NPs, offers a novel approach to the regulation of drug release.[148]

Cesar et al prepared CS-5-ASA by coupling mesalazine (5-ASA) and CS. The CS-5-ASA was selected for the intestinal environment and acted as an adhesive in the colon. This finding suggested that the nanoparticle could be used as an alternative therapy for UC.[154] Egg white-derived peptides (EWDP) and hydrophobic quercetin were encapsulated into oral colon-targeting NPs by using Zein/CS templates. EWDP co-assembled with the actively targeting CS polymers, promoting enhanced colon-specific accumulation of the NPs. This targeted delivery significantly repaired the intestinal barrier and restored gut microbiota balance.[155] Wang et al investigated the potential of CS-Zein NPs in the delivery of magnolol to enhance the anti-inflammatory effects of colon inflammation. The findings revealed that the help of NPs resulted in enhanced Mag accumulation in the inflamed colon and improved cellular uptake. Further, in vivo studies demonstrated that the use of this nanoparticle in conjunction with a hydrogel modulated cytokine expression levels, leading to the treatment of colitis and the restoration of the mucosal barrier in mice.[156] Chen et al reported the synthesis of EGCG-PVP-CS (EPC) by conjugating epigallocatechin gallate (EGCG) with poly(*N*-vinylpyrrolidone) (PVP) and the polysaccharide CS. This formulation enhanced the antioxidant capacity of the natural polyphenol EGCG. Both in vivo and in vitro experiments demonstrated that EPC exhibited strong reactive oxygen species (ROS) scavenging activity and effectively inhibited colitis in a mouse model of UC. These findings provide valuable data supporting the potential clinical application of polyphenols in the treatment of inflammatory diseases.[157] Gou et al demonstrated that surface modification of curcumin-loaded NPs with CS enabled targeted delivery of curcumin to macrophages, resulting in enhanced anti-inflammatory effects. Animal studies further confirmed that this CS-modified nanocarrier exerted a therapeutic effect in alleviating symptoms of UC.[158] Jiang et al highlighted the importance of CS-based targeting strategies for the treatment of colitis. Upon surface modification with CS, tetrasulfide-containing organosilica NPs (DSMSNs) not only improved the solubility of resveratrol (Res) and enhanced its cellular uptake but also facilitated its release in the intracellular environment. The observed alleviation of colitis symptoms in a disease model supported this approach as a novel concept for the oral treatment of UC.[159]

Matos Oliveira et al immobilized TNF-α antibodies onto CS/PAMAM dendrimer NPs. The combined anti-TNF-α activity of the CS and antibodies, demonstrated in inflammatory models, offers a promising therapeutic strategy for various inflammatory conditions, including rheumatoid arthritis.[149] Zewail et al encapsulated leflunomide nanocapsules (NCAPs) with CS, resulting in a higher maximum concentration (Cmax), greater area under the curve (AUC), and lower TNF-α levels compared to the formulations encapsulated with chitosan. The dual advantages of CS-inherent anti-inflammatory properties and active targeting capability enabled CS-coated NLCs to exhibit promising anti-inflammatory potential in a rat model of rheumatoid arthritis.[160] Sun et al reported that grafting CS onto the surface of curcumin-tragacanth gum-gelatin composite nanocapsules (TGNCs) enabled targeted delivery to macrophages, leading to enhanced cellular uptake. This modification resulted in superior accumulation at joint sites compared to the NPs without CS. In the treatment of rheumatoid arthritis, CS-Cur-TGNCs promoted the polarization of macrophages from M2 phenotype to M1 phenotype, while simultaneously reducing the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Moreover, this strategy significantly alleviated joint swelling in a gouty arthritis (GA) rat model.[30]

Bishnoi et al conjugated CS to a non-targeted nanovesicle formulation (MB-NV) to develop a sublingual formulation, C-MB-NV, with targeted delivery.[150] This formulation enabled the sublingual administration of tapentadol HCl, effectively bypassing first-pass effects. It demonstrated improved pharmacokinetic parameters compared to the non-targeted formulation, reducing the risk of addiction and providing sustained analgesic effects. This study offers preclinical data supporting the use of this approach in the treatment of osteoarthritis. Yin et al reported that the addition of CS to the surface of platinum NPs (ptNPs) enhanced their biocompatibility with osteoarthritic chondrocytes. This environmentally friendly nanoparticle preparation method, which avoids the use of harmful chemicals, shows significant potential for the treatment of osteoarthritis.[161] Qu et al synthesized polyethyleneimine (PEI)-modified CS derivatives (PEI-CS) for the targeted delivery of oligodeoxyribonucleotide (ODN) YW002. This nanoparticle effectively protected ODN YW002 from premature inactivation, reduced the expression of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α in RAW246.7 cells, and demonstrated the ability to inhibit periodontitis in mice. These findings suggested that PEI-CS NPs had significant potential as a therapeutic approach for the treatment of periodontitis.[151] Notably, CS-based nanoplatforms have shown broad potential in anti-inflammatory therapies, an area that has become a prominent focus of research. However, to maximize their therapeutic effectiveness, strategies are needed to overcome the limitations of single therapeutic modalities.

Emerging research trends indicate that integrating synergistic approaches could enhance anti-inflammatory efficacy. For instance, He et al reported that methacrylated gelatin-magnetic nanocomposites, when combined with laser irradiation, significantly reduced levels of key pro-inflammatory factors such as TNF-α and IL-1β. This finding may offer valuable insights for advancing anti-inflammatory applications.[162]

CS-Based Nanoplatform in Tissue Engineering

The ECM consists of a complex network of proteins, proteoglycans, and other biomolecules.[163] The combination of NPs with ECM-based materials can more effectively facilitate drug targeting and promote tissue-specific cell differentiation, offering significant benefits for tissue engineering development.[163] Polymer-based scaffolds have been utilized to enhance tissue regeneration by mimicking the physical properties of native tissues.[164] The intrinsic biochemical cues of ECM-derived materials can enhance nanoparticle-targeted drug delivery and provide additional bioactivity for wound healing and regenerative medicine.[163] CS, as a component of the ECM, plays a crucial and dynamic structural role within the matrix.[165] CS can be integrated with nanofiber scaffolds to simulate the ECM environment of cartilage, thereby maintaining the chondrocyte phenotype while promoting cell adhesion, proliferation, and ECM secretion. For instance, a nanofiber scaffold composed of poly(vinyl alcohol) and bio-inspired CS, with fibers at the nanoscale, has been applied for articular cartilage repair.[166] Compared to traditional particle culture, this nanofiber scaffold not only enhanced the chondrogenic differentiation of mesenchymal stem cells but also increased ECM production and the expression of cartilage-specific genes, while supporting cell proliferation. The improved formation of cartilage tissue observed with this scaffold underscores its potential in articular cartilage repair.[166] Furthermore, 3D electrospun nanofiber scaffolds have been developed for cartilage regeneration. Chen et al advanced this approach by crosslinking CS onto the 3D scaffold. This functionalization leverages CS's excellent properties in promoting cartilage regeneration and its potential in immune regulation.[167]

CS-based nanofiber scaffolds have promising applications in wound healing. Researchers have prepared a polyelectrolyte complex using chitosan and CS, which formed an in-situ scaffold via spontaneous mixing. This scaffold demonstrates excellent blood compatibility and potent antibacterial activity, while simultaneously stimulating fibroblast proliferation to facilitate wound healing, positioning it as an ideal candidate for wound dressings.[168] Place et al reported that polyelectrolyte composite nanoparticles (PCNs) formed by the complexation of anionic and cationic polysaccharides could effectively simulate the function of aggrecan.[169] The cationic polysaccharides chitosan and *N, N, N*-trimethyl chitosan (TMC) are complexed with the anionic GAGs heparin (Hep) and CS in solution with the polyanion in excess. The resulting PCNs have a colloidally stable, negatively charged structure that closely mimics the size and chemical characteristics of aggrecan. CS-based aggrecan mimetics are as effective as aggrecan, and these PCNs can be applied either in soluble form or bound to surfaces for targeted growth factor delivery. This strategy holds significant promise for enhancing the therapeutic delivery of Hep-binding growth factors and cytokines in tissue engineering and wound healing applications.

Due to its inherently low mechanical strength and limited load-bearing capacity, CS is often combined with other materials, thereby broadening its range of applications. However, the synthesis of CS-based NPs typically involves complex chemical modifications and processing steps, which raise production costs and present technical challenges. Future research should focus on developing more efficient preparation methods to enhance the applicability of CS-based nanoplatforms in bone repair and wound healing.

CS-Based Nanoplatform in Biological Sensing

CS can participate in the construction of biosensors based on a series of nanomaterials, such as gold NPs (AuNPs) and quantum dots. It can be used as a recognition element or stabilizer for the detection of biomolecules, especially some tumor markers. For example, CS can be modified on the surface of AuNPs. AuNPs have excellent performance, high sensitivity, simplicity, and low cost in colorimetric detection, and can be used as colorimetric probes for detecting chemicals, ions and biomolecules. Noh et al demonstrated that CS-reduced AuNPs (CS-AuNPs) could be effectively used for melamine detection in infant formula, offering rapid and reliable sensing capabilities.[170] CS has negatively charged groups that interact with cations, especially metal cations. Therefore, it could be an asset in the development of new materials for the detection, extraction, or separation of heavy metals. For example, Santos et al reported that metal cation optosensing membranes were improved through the incorporation of sulfated polysaccharides. It has a stronger

interaction with metal cations and can form more chromophore complexes, ultimately leading to an increase in the intensity signal given by the complex formation.[171] The photosensitive film with CS added exhibited a low detection limit and excellent selectivity for detecting heavy metals. Xu et al developed an antifouling electrochemical biosensor based on CS-functionalized polyaniline (CS/PANI) and DNA-peptide conjugates, capable of directly detecting cortisol in bodily fluids such as sweat, saliva and tears.[172] The antifouling properties of CS, combined with its interaction capabilities, improved the biosensor's sensitivity and performance in biological environments. Additionally, Zhao et al developed of a novel electrochemical biosensor based on Fe_3O_4@Au@polyethylene glycol (PEG)@CS NPs.[173] This biosensor demonstrated ultra-low pollution characteristics in complex biological systems, along with high selectivity, reproducibility and storage stability. Notably, it was successfully used to detect Mycoplasma pneumoniae in whole serum, showcasing its clinical diagnostic potential.

Dysregulation of glycosaminoglycan (GAG)-cleaving enzymes in vivo is associated with numerous human diseases, including cancer, diabetes, atherosclerosis, arthritis, inflammation, and cardiovascular disorders.[174] CS can be covalently conjugated to fluorescent dyes and subsequently immobilized onto AuNPs to construct nanosensors that serve as excellent substrates for GAG lyase.[174] Upon treatment with GAG lyase, these nanosensors release dye-labeled oligosaccharides or disaccharides from the AuNPs, thereby enhancing fluorescence recovery. These nanosensors can serve as diagnostic tools for detecting dysregulation of GAG cleavage enzyme expression. Furthermore, CS-based biosensors have scientific significance and applications in seawater aquaculture and the prevention of foodborne diseases. The amino groups in CS exhibit strong proton-accepting capabilities, enhancing hydration upon protonation and forming a dense hydration layer that improves the material's antifouling performance. For instance, an antifouling electrochemical biosensor was developed by using CS-functionalized polyaniline (CS/PANI) combined with DNA-peptide conjugates, enabling the direct assay of cortisol in human fluids.[172] The inherent antifouling properties of both CS and the DNA-peptide conjugates contribute to the biosensor's exceptional detection sensitivity.

CS-based NPs are well-suited for the real-time monitoring of biomarkers such as glucose, proteins and nucleic acids, and are widely employed in disease diagnosis and health data monitoring. However, in complex biological samples, interfering components can compromise the detection signal. Therefore, enhancing the selectivity of CS-based NPs remains a critical issue in biosensing applications for further improvement.

Conclusions

Overall, significant progress has been made in disease therapy, tissue repair and biosensing through the use of CS-based nanoplatforms. These platforms not only complement the shortcomings of chemotherapy but also help reduce tumor cell drug resistance. Their unique physicochemical properties, including targeted delivery, redox and pH responsiveness, and sensitivity to enzymes and other environmental factors, have enabled them to exhibit superior anti-tumor potency in specific therapies. Moreover, the integration of emerging strategies has considerably expanded the potential of these nanoplatforms in synergistic treatment approaches.

In addition to their applications in anti-tumor therapy, CS-based nanoplatforms showed promising prospects for treating ophthalmic diseases, liver diseases, neurodegenerative disorders and various inflammatory conditions. These studies suggested that CS nanoplatforms not only served as effective drug carriers that enhanced therapeutic efficacy but also exerted synergistic effects through their inherent anti-inflammatory properties. Furthermore, integrating CS with nanofibrous scaffolds offered innovative solutions for cartilage repair and wound healing. Interestingly, the incorporation of CS into biosensors enabled the accurate monitoring of trace substances and their expression, highlighting its significant potential for practical applications.

Despite the promising results observed in experimental studies, extensive clinical trials are necessary to validate the transition of CS-based nanoplatforms from the laboratory to clinical applications. The unique properties of CS extend beyond cancer treatment, warranting exploration of its potential in other medical fields. Future research should focus on designing comprehensive clinical trials to thoroughly assess the safety, efficacy, and feasibility of these nanoplatforms, thereby providing robust data to support the development of anticancer therapies and treatments for other diseases.

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Disclosure

The authors report no conflicts of interest in this work.

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