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Review

Hyaluronic acid-based nanoplatforms for Doxorubicin: A review of stimuli-responsive carriers, co-delivery and resistance suppression

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Abbreviations: ABC, ATP-binding cassette; ADH, adipic acid dihydrazide; AHA, aldehyde HA; BBB, blood-brain barrier; BTB, blood-tumor barrier; CS, chitosan; CuS, copper sulfide; CDs, carbon dots; CSCs, cancer stem cells; CP, cisplatin; DOX, doxorubicin; EPR, enhanced permeability and retention; ECM, extracellular matrix; EMB, mbelin; EMT, epithelial-to-mesenchymal transition; EDC, 1-ethyl-3(3-dimethylaminopropyl)carbodiimide; EVs, extracellular vesicles; GSH, glutathione; GA, glycyrrhetinic acid; GO, graphene oxide; GEM, gemcitabine; HA, hyaluronic acid; LA, lipoic acid; Lys, lysine; miRNAs, microRNAs; MSNs, mesoporous silica nanoparticles; MR, magnetic resonance; MP, mercaptopurine; MTX, methotrexate; NIR, near infrared; P-gp, P-glycoprotein; PMs, polymeric micelles; ROS, reactive oxygen species; RBITC, rhodamine B isothiocyanate; siRNA, small interfering RNA; SphK1, sphingosine kinase 1; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; pTRAIL, plasmid TRAIL; TPP, triphenyl phosphonium; TPGS, D-alpha-tocopheryl polyethylene glycol 1000 succinate; 3′-UTR, 3′-untranslated region; UV, ultraviolet; VES, vitamin E succinate.

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ABSTRACT

An important motivation for the use of nanomaterials and nanoarchitectures in cancer therapy emanates from the widespread emergence of drug resistance. Although doxorubicin (DOX) induces cell cycle arrest and DNA damage by suppressing topoisomerase activity, resistance to DOX has severely restricted its anti-cancer potential. Hyaluronic acid (HA) has been extensively utilized for synthesizing nanoparticles as it interacts with CD44 expressed on the surface of cancer cells. Cancer cells can take up HA-modified nanoparticles through receptor-mediated endocytosis. Various types of nanostructures such as carbon nanomaterials, lipid nanoparticles and polymeric nanocarriers have been modified with HA to enhance the delivery of DOX to cancer cells. Hyaluronic acid-based advanced materials provide a platform for the co-delivery of genes and drugs along with DOX to enhance the efficacy of anti-cancer therapy and overcome chemoresistance. In the present review, the potential methods and application of HA-modified nanostructures for DOX delivery in anti-cancer therapy are discussed.

1. Introduction

Different strategies are currently utilized in anti-cancer treatment, including surgery, chemotherapy, targeted therapy, radiotherapy and immunotherapy. Surgery is commonly conducted for early-stage and less aggressive tumors, but is not very useful for advanced metastatic tumors. Chemotherapy is one of the most common methods used to kill cancer cells and treat advanced tumors (Ashrafizadeh, Najafi, Makvandi, et al., 2020; Bagheri et al., 2020; Khatami et al., 2021; Poh et al., 2019). Chemotherapy is preferred over surgery because of its non-invasive or minimally-invasive nature. Accordingly, an extensive array of chemotherapeutic agents such as cisplatin, paclitaxel, docetaxel and doxorubicin (DOX) have been developed for cancer chemotherapy (Abu Samaan et al., 2019; Ashrafizadeh, Zarrabi, Hashemi, et al., 2020a; Ashrafizadeh, Zarrabi, Hashemi, et al., 2020b; Ashrafizadeh, Zarrabi, Hushmandi, et al., 2020; Clarke et al., 2019; Dai et al., 2016; Li, Zhan, et al., 2019; Swamy et al., 2017; Zhang, Sui, et al., 2020). Nevertheless, the aforementioned chemotherapeutic agents have not been completely successful in clinical studies. Several important questions arise regarding treatment failure. For instance, in the treatment of brain tumors, blood-brain barrier (BBB) prevents the entry of chemotherapeutic drugs to the brain (Arvanitis et al., 2020). Cancer cells also form a blood-tumor barrier (BTB) that restricts the penetration of anti-cancer drugs into tumor tissues (Chen, Zeng, et al., 2019). Anti-tumor agents often suffer from poor bioavailability. High doses of these chemotherapeutic agents are often undesirable because of their concentration-dependent toxicity (Ashrafizadeh, Zarrabi, Hashemi, et al., 2020a; Ashrafizadeh, Zarrabi, Hashemi, et al., 2020b; Varela-López et al., 2019). More importantly, the frequent application of chemotherapeutic drugs often results in the emergence of a phenomenon known as “drug-resistance” (Abd-Rabou et al., 2020; Manu et al., 2014; Manu et al., 2015; Poh et al., 2019).

Over the last couple of decades, scientists have been actively searching for additional methods to improve the efficacy of cancer chemotherapy. Much effort has been devoted to increase the anti-tumor activity of chemotherapeutic agents (Manu et al., 2012; Rajendran, Ong, et al., 2011). Taking into consideration the difficulties associated with cancer chemotherapy such as chemoresistance, poor bioavailability and presence of the BBB and BTB, it appears that nanotechnology may be a viable option for improving the efficacy of cancer chemotherapy. Increasing evidence demonstrates the potential of nanostructures in enhancing the bioavailability of anti-cancer agents, enabling targeted delivery and allowing penetration into BBB and BTB (Curley et al., 2020; Le Floc'h et al., 2020). Nanoparticles may be modified by other agents to promote their targeted delivery (Chiesa et al., 2018; Lu, Luo, et al., 2020; Naserifar et al., 2020).

In the present review, we focus on delivery of DOX using hyaluronic acid (HA)-modified nanostructures. The reason for choosing DOX is its wide application in cancer treatment and frequency of resistance that novel strategies should be deployed in this case. Furthermore, among anthracycline members, DOX application in cancer therapy in more common compared to daunorubicin, epirubicin, idarubicin, mitoxantrone and valrubicin. Therefore, we allotted this review to investigating potential application of HA-modified nanostructures in DOX delivery. Overall, we first introduce chemistry and biology of HA. This will be followed by discussion on the application of DOX in anti-cancer therapy and review of its mechanisms of resistance. HA-based functionalized materials designed for DOX delivery, co-delivery of DOX with genes or anti-tumor drugs, including their applications in theranostic will then be critically analyzed.

2. Structure and properties of HA: chemistry and biology

2.1. Chemistry aspect

HA is a natural linear polysaccharide consisting of D-glucuronic acid and *N*-acetyl-D-glucosamine units (Fig. 1) (Cai et al., 2019; Luo et al., 2019; Zhai et al., 2020). This polysaccharide was first isolated from the bovine eye in 1934, and its molecular weight is dependent on the length of the chains (Wickens et al., 2017). HA is a hydrophilic polysaccharide and attracts moisture due to the abundant presence of hydroxyl groups. It can bind to water molecules via hydrogen bonds. The functional groups on HA such as carboxyl, hydroxyl, and acetamido can be employed for chemical modification (Zuber et al., 2011). For example, researchers have developed HA derivatives including dopamine-HA (Texidó et al., 2017) and methacrylate-HA (Gwon et al., 2017) with diverse biomedical applications. As an anionic polysaccharide, HA is biodegradable and biocompatible, leading to significant applications in biomedicine (Choi et al., 2012).

HA is the main component of the extracellular matrix (ECM) exclusively found in skin, synovial fluid, and vitreous humor (Fig. 1) (Lee & Spicer, 2000). While a variety of sources including animal tissues, microbial production systems or synthetic enzymatic reactions have been deployed for the preparation of HA, commercial HA is commonly obtained from animal sources (Liu et al., 2011; Sze et al., 2016). Deprotonation of the functional groups of HA occurs under physiological conditions due to the pKa = 3–4 of the carboxyl groups of HA (Huang & Huang, 2018). HA is a hydrophilic agent and can form viscous and elastic gels by binding to water (Payne et al., 2018). Membrane-bound HA synthase enzymes are responsible for the biosynthesis of HA, and the resulting HA can have a molecular weight in the range of 5–20,000 kDa (Cowman & Matsuoka, 2005; Itano et al., 1999).

2.2. Biological aspect

HA nanoparticles are valuable candidates in the field of biomedicine. There are reactive sites on the HA molecule, including carboxylic groups, hydroxyl groups, and -$NHCOCH_3$ groups that have the potential for covalent modification; carboxylic group can be used for chemical modification by amination or esterification (Jiang et al., 2019; Liu, Liang, et al., 2020). HA-based nanoscale delivery systems have been extensively applied in cancer therapy due to the affinity of HA in binding

to CD44 molecules expressed on the surface of cancer cells (Kim et al., 2019). CD44 is a multifunctional cell surface glycoprotein involved in the proliferation, migration and angiogenesis. Recently, selenium and dopamine-crosslinked HA hydrogels were prepared for breast cancer chemotherapy. Selenium is capable of triggering dopamine polymerization by providing an alkaline pH and interacting with functional groups of HA, and can inhibit cancer proliferation and survival via a pro-oxidant effect (Yang, Lee, et al., 2020). HA-modified selenium nanoparticles have been applied for the delivery of paclitaxel in cancer therapy. HA enables targeted delivery and cellular uptake by lung cancer cells via clathrin-mediated endocytosis. Suppression of proliferation and invasion has been observed following treatment with HA-modified selenium nanoparticles (Zou et al., 2019). The benefits of HA nanoparticles are their stability and biocompatibility (Xu et al., 2020). HA nanoparticles are internalized into cells due to their binding to CD44, making them potential candidates to suppress cancer progression (Wang, Liu, et al., 2020).

3. Cancer resistance mechanisms: DOX and role of HA

3.1. Doxorubicin and resistance mechanisms

DOX is an anthracycline antibiotic with brand name Adriamycin, which is extensively deployed in the treatment of different hematological and solid tumors (Ashrafizaveh et al., 2021; Mohajeri & Sahebkar, 2018). DOX is isolated from *Streptomyces peucetius*, and structurally, DOX possesses an amino sugar and four rings typical of an anthraquinone structure (Chao Chen, Lu, et al., 2018). The major anti-cancer mechanisms of DOX, include the suppression of topoisomerase II activity and intercalation with DNA thus preventing cell replication and enhancing generation of free radicals (Meredith & Dass, 2016). DOX is popular in cancer therapy due to its low cost and diverse applications to various types of cancers (Rajendran et al., 2012; Rajendran, Li, et al., 2011; Shishodia et al., 2007). However, the benefits of DOX administration are limited due to the development of resistance in cancer cells (Zhang, Zhou, et al., 2019). Consequently, different approaches such as changing the type of chemotherapy delivery route, combination therapy with other anti-tumor agents, gene therapy and the use of nanocarriers have been proposed for improving the efficacy of DOX in cancer therapy (Guo et al., 2020; Wang, Luo, et al., 2019; Yang, Li, et al., 2020).

It appears that the reduced intracellular accumulation of DOX in cancer cells is also responsible for developing DOX resistance. The anti-tumor agents such as imatinib, curcumin and canagliflozin are capable of promoting DOX sensitivity via down-regulation of the P-gp as a drug efflux pump, and enhancing the cellular uptake of DOX (Chen, Liu, et al., 2019; Yang, Li, et al., 2020; Zhong et al., 2020). Cancer stem cells (CSCs) are considered as potential targets in cancer therapy, as they can participate in chemoresistance and aggressive behavior of cancers (Duan et al., 2021). DOX administration eradicates non-side population of thyroid cancer cells that is beneficial for CSCs as they can grow easily and without competition. Noteworthy, CSCs are able to induce DOX resistance via upregulation of drug transporters such as MDR1 and/or ABCG2 (Zheng et al., 2010). Non-coding RNAs (ncRNAs), especially microRNAs (miRNAs) play a significant role in triggering DOX resistance. For instance, exosome-mediated delivery of miRNA-223 to gastric cancer cells mediates their DOX resistance via F-box and WD repeat domain-containing 7 (*FBXW7*) down-regulation (Gao et al., 2020). Besides, miRNA-21 induces DOX resistance in prostate cancer cells (PC3 cells) via down-regulation of phosphatase and tensin homolog (PTEN) as a tumor-suppressor factor (Zhao et al., 2021).

Nanoparticles are promising candidates for enhancing the anti-tumor activity of DOX against cancer cells and preventing chemoresistance (Coelho et al., 2019; Pishavar et al., 2019; Zhang, Jia, et al., 2019). Increasing DOX internalization in cancer cells, reducing IC_{50} value of DOX and co-delivery option are benefits of using nanoparticles for DOX delivery in cancer suppression (Ashrafizadeh, Zarrabi, Hashemi, et al., 2020a; Ashrafizadeh, Zarrabi, Hashemi, et al., 2020b). For example, DOX- and edelfosine-loaded lipid-polymer hybrid nanostructures are able to mediate synergistic impact in suppressing chemoresistance feature of osteosarcoma (Yang, Zhang, et al., 2020). Besides, gold nanoparticle-mediated hyperthermia effectively kills colorectal cancer cells and increases their DOX sensitivity (Roma-Rodrigues et al., 2020). The present review aims to discuss the role of HA-modified nanoarchitectures in the delivery of DOX, and exploitation of this strategy in improving current cancer chemotherapy.

3.2. HA and DOX combination in synergistic cancer therapy

For exerting its anti-tumor activity, a certain chemotherapeutic agent such as DOX should first penetrate into cancer cells and then, affect cytoplasmic organelles and make other alterations in nucleus, if necessary. However, there are receptors on cell membrane such as P-glycoprotein (P-gp) belonging to ATP-binding cassette (ABC) family, that can induce drug efflux, leading to chemoresistance (Liu, Bai, et al., 2020; Liu et al., 2021). For overcoming DOX resistance, reducing activity and expression of P-gp are of importance (Wang et al., 2021). Furthermore, cancer cells obtain resistance to DOX-mediated cell death (apoptosis). Therefore, conjugation or co-administration of DOX and anti-tumor agents can sensitize cancer cells to apoptosis, improving chemosensitivity (Yang, Li, et al., 2020; Zhong et al., 2020). In case of DOX and HA, just one experiment has highlighted role of this combination in synergistic cancer therapy and more studies are needed to evaluate role of HA and its derivatives in increasing DOX's anti-tumor activity and suppressing resistance. HA-curcumin conjugation can promote DOX sensitivity of lung, liver and intestinal cancers via mediating targeted delivery (CD44 receptor) and subsequent down-regulation of P-gp. Furthermore, HA-curcumin conjugation induces apoptosis via mitochondrial pathway in cancers (Diao et al., 2019). This experiment reveals that anti-apoptotic and regulatory impact of HA-curcumin conjugation on P-gp sensitize cancer cells to DOX chemotherapy. However, no certain and absolute conclusion can be made from one experiment and more studies are needed in this case.

3.3. Role of HA-based nanoparticles in suppressing DOX resistance

In the previous section, it was shown that HA-based advanced materials can be used to enhance the intracellular accumulation of DOX and increase its competence in cancer therapy; HA-based nanoscale delivery systems can be deployed to reverse the DOX resistance as their modification with triphenylphosphonium (TPP) assists in targeting the mitochondria. However, DOX-TPP conjugate has an amphiphilic nature and so is difficult to encapsulate within nanocarriers. But the bromide salt of TPP can be used instead for linking to HA via ionic bonds to prepare a supra-molecular self-assembled structure comprising HA, DOX and TPP. These nanoparticles specifically targeted mitochondria to increase reactive oxygen species (ROS) levels and decrease mitochondrial membrane potential, resulting in the suppression of DOX resistance (Liu et al., 2018). This experiment highlights the fact that affecting mitochondria is of interest for activating intrinsic pathway of apoptosis in sensitizing cancer cells to death and suppressing DOX resistance. In order to obtain such potential, agents capable of targeting mitochondria such as TPP, as mentioned before, can be utilized.

HA-based advanced materials can enhance tumor accumulation and improve the anti-tumor activity of DOX while reducing its adverse effects. HA modification significantly enhances the selective targeting of cancer cells and can be further improved using PEGylation to augment the enhanced permeability and retention (EPR) effect (Wang, Li, et al., 2018). Enzymatic degradation of HA mediates the internalization and enhances the accumulation of DOX in colon cancer cells, leading to P-gp down-regulation and the reversal of DOX resistance (Yim & Na, 2010). In fact, the potential of HA-modified nanoparticles in reversing DOX resistance is attributed to targeting tumor-promoting factors such as P-

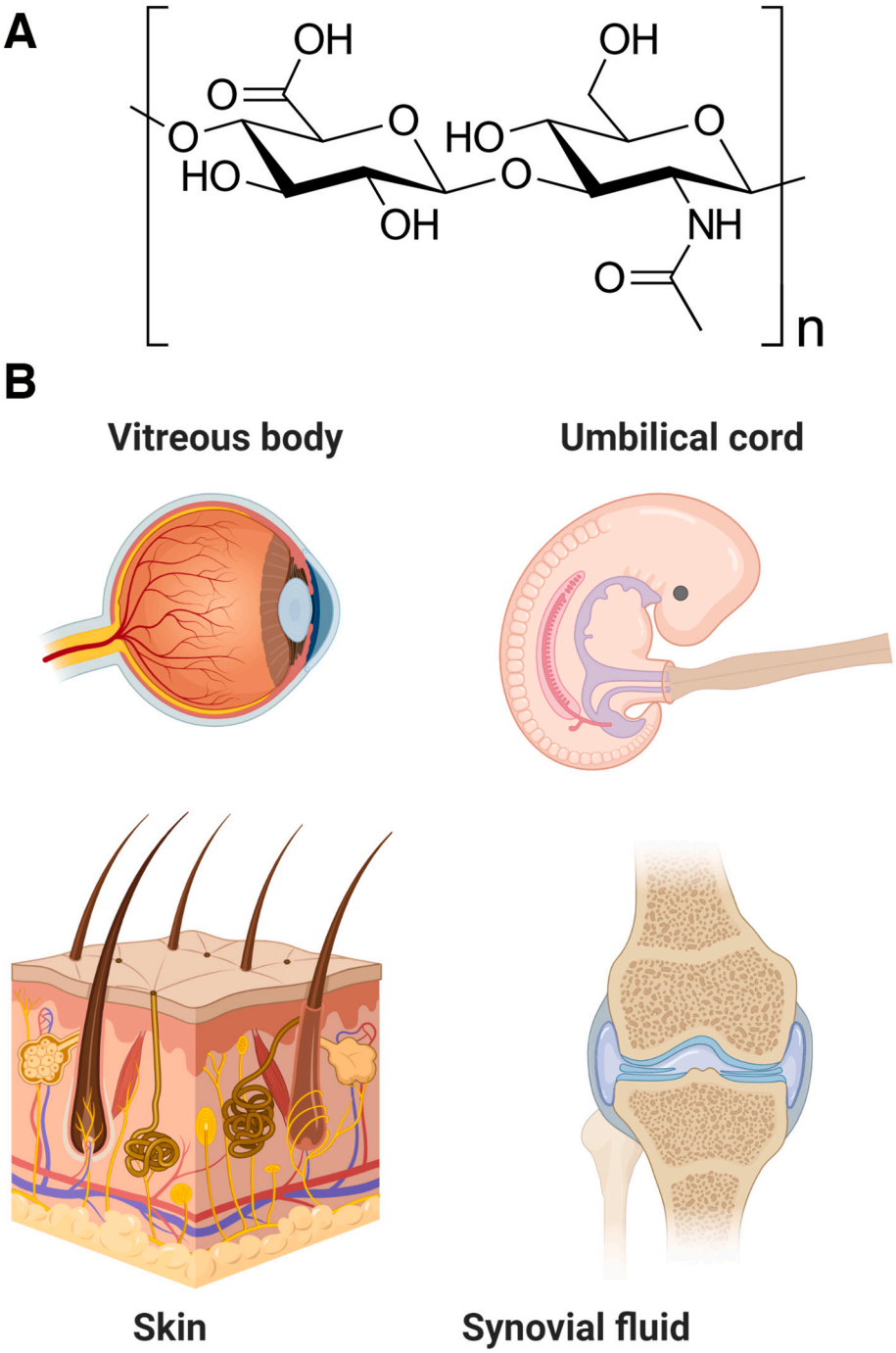

Fig. 1. Structure and occurrence of HA. A. The chemical structure of HA showing a polymer of disaccharides with a glycosidic bond linking the *N*-acetyl-D-glucosamine group with the D-glucuronic acid group. B. Common organs with high levels of HA. HA, hyaluronic acid.

gp, Notch-1 signaling and anti-apoptotic proteins (Bcl-2).

In vivo experiments have confirmed the efficacy of DOX-loaded HA nanocarriers in cancer therapy. Cross-linking HA with lipoic acid (LA)-lysine (Lys) led to the formation of nanoparticles with a size of 152–219 nm. In vivo experiment in nude mice showed an enhanced circulation time of HA-LA-Lys nanoparticles and their accumulation at the tumor site, resulting in the increased anti-tumor activity of DOX and preventing DOX resistance (Zhong et al., 2015). To improve the stability and encapsulation efficiency of HA nanoparticles, other kinds of polymers have been used exemplified by the preparation of HA with vitamin E succinate *co*-polymers (HA-VES) that could be loaded with DOX. They demonstrated superior colloidal stability and high encapsulation efficiency. HA-VES nanocarriers could release DOX into the lysosomes, enabling nuclear delivery, and promoting interactions with DNA, ultimately leading to apoptosis and suppression of DOX resistance (Wang, Ma, et al., 2016). Overall, the following bullet points can be concluded:

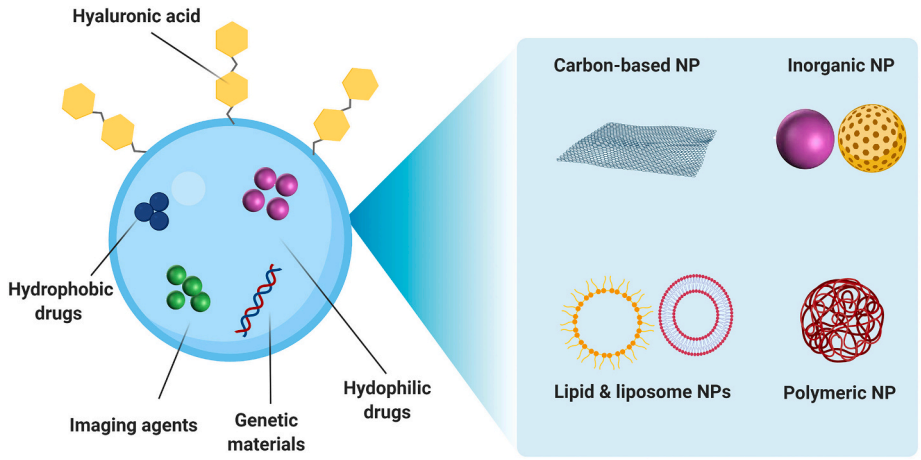

Fig. 2. Different types of nano-sized structures containing a wide variety of cargos have been functionalized with hyaluronic acid to enhance the targeted delivery to tumors. NP: nanoparticle.

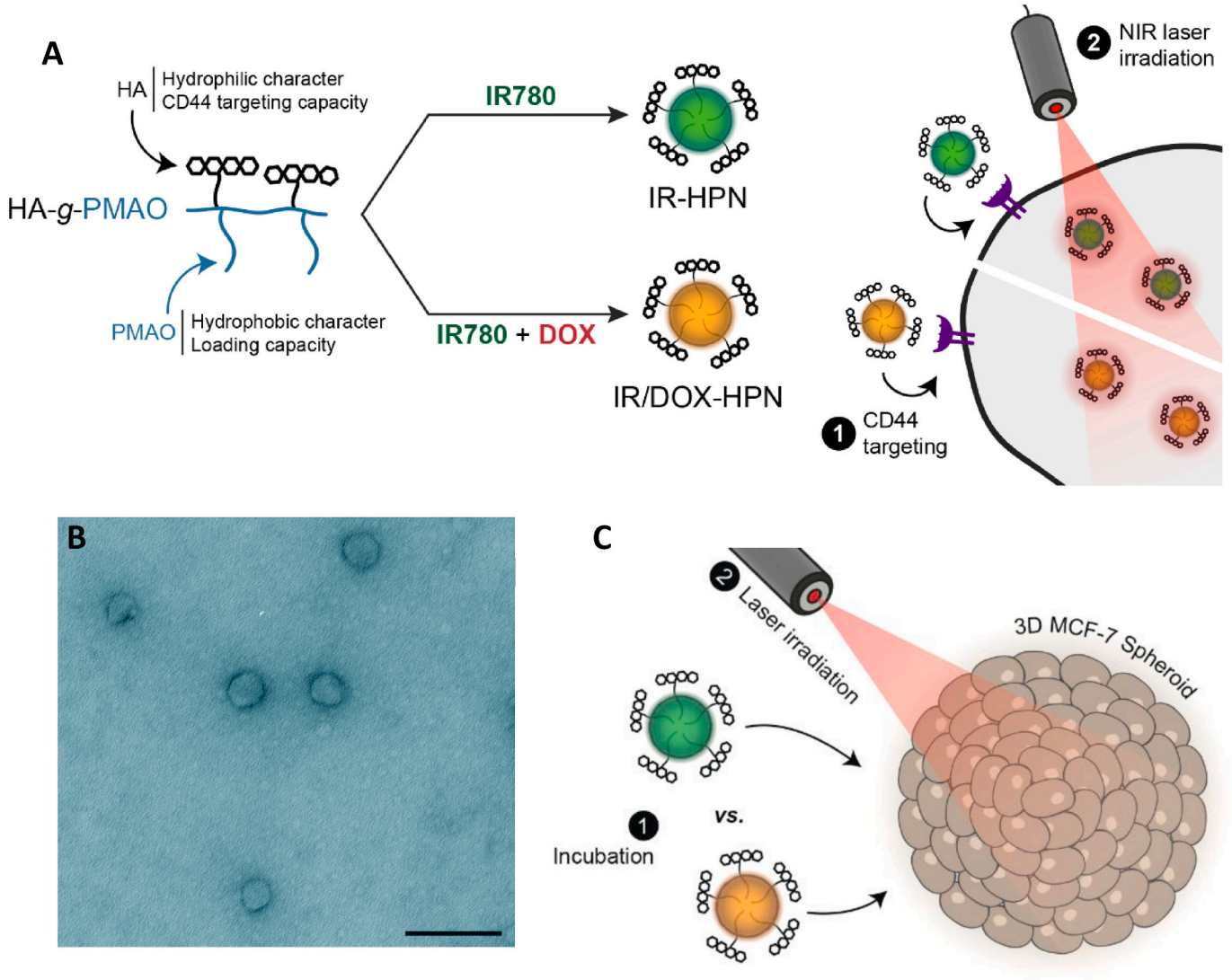

Fig. 3. HA-modified polymeric NPs for DOX delivery. (A) Schematic illustration of polymeric nanoparticles and application in cancer therapy. (B) TEM image of the polymeric nanoparticles. (C) Schematic illustration of the procedures used to evaluate the phototherapeutic effect of polymeric nanoparticles towards 3D MCF-7 spheroids. DOX: doxorubicin; IR780: near-infrared dye; HPN: hyaluronic acid polymeric nanoparticles.
Reprinted from (Alves et al., 2019) with permission from Elsevier.

A) The HA-modified nanoparticles have confirmed their efficiency in overcoming DOX resistance in vitro and in vivo,
B) These nanostructures possess high stability and biocompatibility, but stability can be further improved by conjugation with other agents such as VES,
C) The role of HA-modified nanoparticles in reversing DOX resistance depends on cargo delivery, so that co-delivery of DOX with miRNA-34a suppresses tumor-promoting Notch-1 signaling in inhibiting DOX resistance (Deng et al., 2014; Liu et al., 2019),
D) Activation of apoptosis is a main pathway followed by HA-modified nanoparticles in reversing DOX resistance.

4. Hyaluronic acid-modified nanomaterials

Several nano-sized structures encompassing a wide variety of different cargos have been modified with HA, to improve their targeted delivery (Fig. 2).

4.1. Polymeric nanoparticles

4.1.1. Non-responsive polymeric nanoparticles

Because DOX possesses several adverse effects that are dose-dependent, new approaches are required to reduce its toxicity on normal cells and tissues. The administration route can be a determining factor as the highest toxicity of DOX is observed with systemic administration. Consequently, there have been efforts to develop nanoparticles for the oral delivery of DOX and increasing its bioavailability and anti-tumor activity, while a simultaneous decrease in side effects is provided. Recently, catechol-modified CS/HA nanoparticles have been assessed for the topical delivery of DOX for oral cancer treatment; catechol and chitosan facilitated the adhesion of nanoparticles to the oral mucosa. The conjugation of HA and CS was performed using an ion gelation method to generate particles of 160 nm in size with a loading capacity as high as 250 mg/mg. These nanoparticles released DOX in a prolonged manner to enhance its cellular uptake, leading to the induction of apoptosis in cancer cells (Pornpitchanarong et al., 2020). Therefore, mucoadhesive polymers should be conjugated to DOX-loaded HA nanoparticles to make them appropriate for oral administration and enhancing DOX cytotoxicity in cancer treatment.

In another study, PEGylated cationic amphiphilic copolymers were prepared and modified with HA to improve their biocompatibility and selectivity towards cancer cells. The DOX release of these nanoparticles occurred following the degradation of HA in endosomes by endogenous hyaluronidase, and subsequent PEG decomposition at the acidic pH of the endosome, resulting in DOX release and cytotoxicity against cancer cells (Fig. 3) (Yan et al., 2019).

HA-based nanoparticles can be further modified to improve some of their properties, such as circulation time and cellular uptake. For instance, glycyrrhetinic acid (GA) was conjugated to the hydroxyl groups of HA to prepare DOX-loaded GA/HA-nanoparticles. These nanoparticles showed an increased circulation time in blood, good cell internalization, and specific targeting to the liver and were tested for the treatment of liver cancer (Wang, Gu, et al., 2018). Overall, HA-polymeric nanoparticles could be promising candidates for DOX delivery, while their toxicity towards normal cells and tendency to aggregation remain as drawbacks (Oommen et al., 2016). However, these nanoparticles have obvious advantages such as high selectivity towards cancer cells, offering sustained release, and enhanced cellular uptake of DOX (Jin et al., 2015; Shahriari et al., 2019). Besides, HA-modified polymeric nanostructures potentiate DOX chemotherapy via increasing its intracellular accumulation and reducing IC_{50} (preventing development of drug resistance after repeated administration). Although a number of studies have used other polymers such as CS and GA for promoting efficacy of HA nanoparticles in DOX delivery, a special attention should be directed towards biocompatibility of these agents. Furthermore, HA nanoparticles cause platelet aggregation at high doses that is a drawback for their clinical application.

4.1.2. Stimuli-responsive polymeric nanoparticles

The tumor microenvironment has a variety of features that differ significantly from normal tissues, an important one being its mild acidic pH (Garg et al., 2020; Moraes et al., 2017). Several anti-tumor drugs and compounds can be negatively affected by this microenvironment. For instance, the mild acidic pH may result in structural alterations in anti-tumor compounds and reduce their efficacy in cancer therapy. Furthermore, the genetic material and nucleic acids can undergo unexpected changes when they are exposed to acidic conditions. Therefore, it is important to protect the normal cellular DNA against acidic microenvironment. Importantly, the acidic tumor microenvironment can be exploited to trigger the release of drugs from pH-responsive nanocarriers.

Recently, spherical core-shell HA-based nanoparticles have been designed for the DOX delivery with a particle size in the range of 167–220 nm. When modified with HA, they could selectively target CD44 overexpressing cells and enable the internalization of DOX in a receptor-dependent manner. Furthermore, these nanocarriers were pH-responsive, showing the preferential release of DOX at an acidic pH. Low toxicity towards normal cells (good biocompatibility) and cytotoxicity against cancer cells suggested that HA-based pH-responsive nanoparticles could be promising agents in cancer chemotherapy (Liao et al., 2018). Some efforts have been made to improve the rate of endocytosis of HA nanoparticles to enhance the uptake into cancer cells. Significant efforts need to be made in reducing their particle size, as most of the HA-based nanostructure tend to have a particle size larger than 150 nm (Tian et al., 2019).

Another strategy to develop smart HA nanoparticles for DOX delivery is to rely on changes in the redox balance. Disulfide-based proteins and small-molecule prodrugs have been synthesized whose release depends on the intracellular GSH levels (Tjin et al., 2017) as their concentrations cause the cleavage of disulfide bonds. For this purpose, GSH-responsive HA nanoparticles containing DOX-D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS) conjugates as prodrugs have been developed. Disulfide bonds are formed between DOX and TPGS, and upon their targeted delivery by HA nanoparticles to tumors, the high GSH levels induce disulfide bond cleavage, leading to DOX release and enhancing anti-tumor activity. It is noteworthy that HA nanocarriers show an encapsulation efficiency as high as 90% (Lu et al., 2019). Macropinocytosis and clathrin-mediated endocytosis are the major pathways used by HA-based nanoparticles for uptake into the cancer cells. Redox-responsive HA nanostructures show a rapid release of DOX for cancer therapy. Furthermore, both in vitro and in vivo studies have confirmed the role of HA-nanoparticles in DOX delivery and cancer therapy (Hu et al., 2016). Due to the high biocompatibility of HA-based advanced nanomaterials, further developments are needed to expand their application into clinical trials.

In addition to the development of smart HA nanoparticles based on internal stimuli such as pH and GSH, external stimuli can be used to trigger the DOX release which can provide superior spatiotemporal control over drug release. This approach can provide multiple dosages from a single administration of drug carrier which can improve patient satisfaction (Timko et al., 2010). Light responsive nanocarriers can be based on polymeric or lipid-based nanostructures (Bansal & Zhang, 2014; Rwei et al., 2015), or inorganic nanoparticles (Huschka et al., 2011; Zhang et al., 2016; Zhong et al., 2014). For instance, light-activated HA-based nanomaterials have been designed for DOX delivery. These degradable nanoparticles were responsive to either near-infrared (NIR) or ultraviolet (UV) radiation. The major component for synthesizing these nanogels was g-7-*N, N*-diethylamino-4-hydroxymethylcoumarin (CM), and for enhancing their selectivity towards cancer cells, they were modified with HA. Exposing the HA-CM nanogels to either NIR or UV irradiation triggered the cleavage of the urethane bond linking HA to CM which subsequently released DOX and

suppressed the breast cancer progression. Because the breast cancer cells express higher levels of CD44, HA modification of nanogels led to their internalization via endocytosis (Hang et al., 2017). A wide variety of experiments have explored role of HA-modified polymeric nanoparticles and their advanced forms for DOX delivery. In order to be stimuli-responsive, a special linkage should be used to degrade by mild acidic pH, redox or light, leading to controlled release of DOX at tumor site.

4.2. Carbon-based nanostructures

The biomedical application of graphene oxide (GO) in cancer therapy is of interest due to its high loading efficiency and hydrophilic oxygenated functional groups that are the key for the surface modification via covalent and noncovalent bonds (Orecchioni et al., 2015; Yang et al., 2008; Zhu et al., 2010). In cancer therapy, GO nanoparticles have been applied for gene and drug delivery, theranostics, as well as photothermal and photodynamic therapy (Choi et al., 2016; Jung et al., 2014; Lu et al., 2009; Tian et al., 2011; Yang et al., 2011). For DOX delivery, HA-Arg-Gly-Asp peptide (RGD)-modified GOs have been developed. These nanocarriers have a loading capacity as high as 72.9% and could release DOX in a sustained manner while still having good biocompatibility. Compared to DOX alone, DOX-loaded HA-RGD GO nanomaterials showed higher cytotoxicity in cancer cells due to their enhanced cellular uptake via CD44 receptor (HA) and integrin (RGD)-induced endocytosis (Guo et al., 2017). Another study prepared a composite of HA-based GO and iron oxide (IO) nanoparticles for DOX delivery and magnetothermal therapy. For this purpose, HA was conjugated to GO through covalent bonding, with good biocompatibility. DOX-loaded GO nanomaterials selectively killed CD44-overexpressing breast cancer cells. In the next step, IO nanoparticles were loaded on the GO nanoparticles to allow magnetic hyperthermia. This combination significantly enhanced the ability of DOX to reduce tumor growth and malignancy (Pramanik et al., 2019). To improve the biocompatibility of HA-based GOs, they can be additionally modified with CS (Yang et al., 2016). Another advantage of nanocarriers is that they can be designed to respond to distinct properties of cancer cells, such as being pH-responsive. Furthermore, by enabling photothermal therapy, HA-based GO nanomaterials can enhance the efficacy of chemotherapy and synergistically increase cancer cell death (Liang et al., 2019; Miao et al., 2013; Song et al., 2014). These experiments reveal a new advantageous of GO nanoparticles in DOX chemotherapy by providing photothermal therapy that can significantly promote its potential in cancer eradication. However, graphene-based nanomaterials suffer from low biocompatibility and introducing HA-modified graphene-based nanomaterials for DOX delivery in clinical course, depends on further modification, for instance by other biocompatible agents such as CS to improve their biocompatibility (Makvandi et al., 2020). Carbon dots (CDs) are newly emerging carbon nanomaterials with good biocompatibility and easy surface modification possibilities (Ashrafizadeh, Mohammadinejad, Kailasa, et al., 2020; Baker & Baker, 2010; Singh et al., 2017). CDs have been applied for gene and drug delivery in cancer therapy (Du et al., 2019; MOHAMMADINEJAD et al., 2020; Panwar et al., 2019). However, it has been reported that unmodified CDs are not suitable to deliver cargos to tumor tissues. Therefore, studies have focused on the surface modification of CDs with various biocompatible agents (such as HA) to promote their selectivity towards cancer cells (Fu, Jang, et al., 2019; Xu et al., 2015). In a recent report, HA-functionalized CDs were prepared using a one-step hydrothermal treatment in the presence of citric acid and branched-PEI as the core carbon source. Then, DOX was loaded on the HA-modified CDs via acid-cleavable bonds and their cytotoxicity was evaluated against breast cancer cells wherein the in vitro and in vivo experiments confirmed the high anti-tumor activity of DOX-loaded HA-modified CDs (Li, Li, et al., 2020). Another study described the preparation of mesoporous silica nanoparticles (MSNs) coated with blue fluorescent *N*-graphene quantum dots, then loaded with DOX, and finally functionalized with HA. These theranostic nanocarriers enabled simultaneous cell imaging while increasing the potential of DOX in cancer cell killing lacking toxicity towards normal cells (Gui et al., 2017). The advantages of CDs are their small size, good biocompatibility, and theranostic potential. However, GO nanomaterials demonstrate some toxicity towards normal cells as shown in different experiments (Gurunathan et al., 2019; Karki et al., 2020; Mohamed et al., 2019). Further use of DOX-loaded HA-modified GO nanomaterials in clinical studies will depend on improved biocompatibility. One of the limitations is that in contrast to other kinds of nanocarriers, experiments have not prepared HA-modified carbon nanomaterials for DOX delivery, an aspect that can be further studied.

4.3. Lipid-based nanoparticles

4.3.1. Non-responsive lipid-based nanoparticles

Liposomes and lipid nanocarriers are often employed in drug and gene delivery due to precise targeting of body organs or tumor sites, including the brain (Pinzón-Daza et al., 2013; Xie et al., 2005). The efficacy of liposomal nanocarriers can be improved by surface modification and subsequent preferential cellular uptake through active or passive mechanisms (Gregoriadis, 1988; Iyer et al., 2006). Passive tumor targeting can be achieved via the EPR effect, and modification of the nanoparticles with ligands recognized by cancer cells can provide active targeting. For this purpose, HA-modified liposomal carriers have been developed for glioblastoma therapy; HA-based nanocarriers could specifically target glioblastoma cells, which over-expressed CD44 on their surface. Subsequently, lysosomal degradation allowed the intracellular delivery of DOX. Interestingly, normal astrocytes and microglial cells showed less co-localization of the nanocarriers in lysosomes suggesting good selectivity for tumor cells (Hayward et al., 2016). It was shown that the cytotoxicity of DOX-loaded liposomes towards normal cells decreased following the surface coating with HA-ceramide (HACE); HACE liposomes can be used for both imaging and drug delivery in cancer therapy. These liposomal carriers can serve as magnetic resonance (MR) imaging probes when loaded with a suitable contrast agent. Besides, HACE-based liposomes released DOX in a sustained manner, with a longer circulation time in blood thus enhancing the anti-cancer effect (Park et al., 2014). Conventional DOX-loaded liposomes show some cardiotoxicity, and their modification with HA significantly improved their biocompatibility. Moreover, HACE conjugation made the liposomes pH-responsive which improved the capacity of targeting cancer cells (Paliwal et al., 2016).

Micelles are another type of lipid-based nanocarrier with extensive applications in cancer therapy. Self-assembled polymeric micelles (PMs) are promising carriers for drug delivery due to their efficiency to encapsulate hydrophobic drugs and their superior tumor targeting capacity (Cabral et al., 2011; Jhaveri & Torchilin, 2014; Torchilin, 2007). Hydrophobic drugs can be loaded into the hydrophobic core of amphiphilic micelles (Domb & Kumar, 2011; Hamaguchi et al., 2005; Matsumura & Kataoka, 2009). Upon systemic administration, micelles owing to their small size can accumulate in tumor tissues with a neovascular capillary network (Maeda, 2010; Maeda & Matsumura, 2011; Matsumura & Maeda, 1986). A study described the preparation of bioreducible core cross-linked HA micelles using D,L-dithiothreitol in aqueous conditions to form disulfide bonds. These PMs displayed high structural stability and good encapsulation efficiency (80%). Due to their stability in the bloodstream, the HA-based micelles accumulated in the tumor site to promote the internalization of DOX. The release of DOX was dependent on glutathione (GSH) levels, as the higher levels of GSH cleaved the disulfide bonds to trigger DOX release (Han et al., 2015). Another study described the conjugation of DOX to a short peptide, known as KIGLFRWR with a self-assembly prowess. Then, to enhance the targeting capacity of these nanoparticles, they were modified with HA. The core-shell structure of the micelles significantly promoted the internalization of DOX in hepatocellular carcinoma cells to suppress their proliferation (Wang, Qian, et al., 2020). HA lipid nanoparticles can enhance cellular

Table 1
HA-based nanomaterials for DOX delivery in cancer therapy.

Nanovehicle	Cancer type	Particle size (nm) Zeta potential (mV) Encapsulation efficiency (%)	Surface modification	Results	Refs
Mesoporous silica nanoparticles	Breast cancer	153.1 nm −9.3 mV	Hyaluronic acid	Improved cellular uptake of DOX by CD44-mediated endocytosis Suppressed cancer growth	(Gupta et al., 2018)
Mesoporous silica nanoparticles	Breast cancer	–	Hyaluronic acid	Excellent therapeutic potential Long blood circulation Accumulation at the tumor site	(Zhan et al., 2021)
Polymeric nanoparticles	Breast cancer	–	Hyaluronic acid	Exerted cytotoxicity against cancer cells Polarized macrophages Changed macrophage phenotype to M1	(Rangasami et al., 2021)
Polymeric nanoparticles	Breast cancer	264.5 nm −16.3 mV	Hyaluronic acid S-nitrosoglutathione	Enhanced ROS levels Apoptosis induction Enhanced cellular accumulation	(Kim et al., 2018)
Protein nanoparticles	Breast cancer	132 nm −38.9 mV 43.2%	Hyaluronic acid	Cellular uptake through CD44-mediated endocytosis Simultaneous imaging and chemotherapy	(Pulakkat et al., 2016)
Mesoporous carbon nanoparticles	Colorectal cancer	350 nm −20.8 mV	Hyaluronic acid	HA functionalization improved selectivity towards cancer cells Suppressed colorectal cancer progression	(Wan et al., 2016)
Polymersomes	Breast cancer	146.2 nm 54.9%	Hyaluronic acid	Excellent biodistribution High anti-tumor activity	(Shahriari et al., 2019)
Iron nanoparticles	Breast cancer	210.3 nm −24 mV	Hyaluronic acid	Enhanced tumor targeting capacity of nanocarriers Eradicated cancer cells and cancer-associated fibroblasts Sustained circulation and high cellular uptake Enhanced potential of DOX in cancer therapy	(Gong et al., 2019)
MOF-iron nanoparticles	Breast cancer	140 nm −25 mV	Hyaluronic acid	Disrupted iron homeostasis in cancer cells Sensitized cell death Ferroptosis induction Increased potential of DOX in cancer eradication	(Xu et al., 2020)
Iron nanoparticles	Breast cancer	48.2 nm −45 mV	Lipid Hyaluronic acid	Due to high cellular uptake, DOX effectively suppressed the progression of cancer cells	(Liang et al., 2020)
Gold nanorods	Breast cancer	55 nm −35.6 mV	Hyaluronic acid	Simultaneous chemotherapy and photothermal therapy Efficiently suppressed tumor growth	(Li, Duy Le, et al., 2019)

uptake of DOX by targeting CD44-overexpressing cancer cells. Conjugation with baicalein, a natural anti-tumor flavonoid, provided a synergistic effect and led to the effective eradication of breast cancer cells (Liu et al., 2016). This experiment highlighted the fact that phytochemicals with anti-tumor activity (baicalein) can be loaded in HA-modified lipid nanoparticles to potentiate anti-tumor activity of DOX. Next experiments can focus on delivery of DOX with other plant derived-natural compounds such as curcumin, resveratrol and berberine using HA-modified lipid nanoparticles.

There are many advantages associated with the use of HA-based lipid nanocarriers for DOX delivery, including enhancing cellular uptake through receptor-mediated endocytosis, promoting DOX bioavailability by overcoming the hydrophobic nature of DOX, preventing drug resistance, and reducing the DOX side effects. Further improvements in the synthesis of smart HA-lipid nanocarriers are continuously being made to enhance the cytotoxicity against cancer cells (Arpicco et al., 2020; Chiu et al., 2020; Duan et al., 2020; Liu et al., 2019; Pornpitchanarong et al., 2020; Wang, Qian, et al., 2020; Xu et al., 2021; Zheng et al., 2017). Table 1 summarizes assorted HA-based nanomaterials that have been deployed for DOX delivery in cancer therapy.

4.3.2. Stimuli-responsive lipid-based nanoparticles

HA-modified nanoparticles can release DOX in a mildly acidic pH (5.0) in a sustained-release manner (Gurav et al., 2016). One strategy uses covalent conjugation for the formation of Schiff base bonds between DOX and HA in nanostructures. DOX has a hydrophobic nature and is loaded into the hydrophobic core, while HA being a hydrophilic compound used as the shell. The DOX release from pH-responsive nanocarriers occurred at pH 5.0 with only minimal release at pH 7.4, affirming the ability of HA-based advanced materials to transport DOX for cancer therapy (Hu et al., 2017).

Other experiments have applied a redox-responsive HA-ibuprofen prodrug containing micelles for DOX delivery to treat metastatic breast cancer. The HA-ibuprofen conjugate is sensitive to a reducing environment and the conjugation was performed by attaching ibuprofen to an HA backbone through disulfide bonds. This prodrug could self-assemble into micelles and showed advantages including high cellular uptake, good biodistribution and was responsive to redox stimulus (Chai et al., 2020). HA nanoparticles can be designed so they are dually responsive to both GSH and pH. Recently, self-assembled micelles were developed by HA-6-mercaptopurine (MP) conjugation; MP has a hydrophobic nature, while HA is hydrophilic. DOX was loaded into the core of the nanocarriers, and the activity against cancer cells and cancer stem cells (CSCs) was evaluated. HA nanoparticles were internalized in a CD44-dependent manner as a CD44-antibody prevented their internalization. The HA nanoparticles induced cell cycle at the G0/G1 phase in colon cancer cells. Due to their GSH-responsive and pH-responsive nature, HA nanocarriers could significantly promote the DOX delivery for cancer therapy (Debele et al., 2018). However, we are still at the initial stages of developing smart nanocarriers for DOX delivery and more studies are needed before transitioning to clinical trials. The experiments have focused on developing smart HA-modified micelles for DOX delivery and more studies are required role of advanced HA-modified liposomes in DOX delivery. Then, a comparison between their potential in delivery and suppressing cancer progression can be made.

4.4. Inorganic nanostructures

4.4.1. Non-responsive inorganic nanoparticles

Inorganic nanoparticles are promising candidates for the delivery of DOX as the surface modification of these nanocarriers can significantly improve their selectivity towards cancer cells. Recently, hybrid nanoparticles containing organic and inorganic materials have been developed for DOX delivery. Metal-organic frameworks (MOFs) have

Table 2
Smart HA-based nanomaterials for DOX delivery in cancer therapy.

Nanovehicle	Sensitive type	Cancer type	Particle size (nm) Zeta potential (mV) Encapsulation efficiency (%)	Drug or gene	Surface modification	Remarks	Refs
HA-based micelles	Reduction-sensitive	Lung cancer	259.6 nm −28.3 mV 63.03%	Doxorubicin	Hyaluronic acid	High biocompatibility Enhanced cellular uptake due to CD44-mediated endocytosis Increased chemotherapy efficacy	(Debele et al., 2018)
Hollow-mesoporous silica nanoparticles	Redox-responsive	Breast cancer	232 nm −23.9 mV	Doxorubicin	Hyaluronic acid	Suppressed tumor proliferation Apoptosis induction	(Huang et al., 2018)
Polymeric nanoparticles	GSH-sensitive	Lung cancer	172.3 nm 90%	Doxorubicin	Hyaluronic acid TPGS	Reduced cell viability as much as 80% Inhibited tumor growth	(Lu et al., 2019)
Liposomes	Redox-responsive	Osteosarcoma	165.3 nm −28.9 mV 91.3%	Doxorubicin	Hyaluronic acid	Burst release of DOX (60%) in the presence of GSH Long blood circulation Cytoplasmic delivery of cargo	(Chi et al., 2017)
Micelles	Redox-responsive	Breast cancer	170 nm −25 mV	Doxorubicin Ibuprofen	Hyaluronic acid	Desirable biodistribution Favorable anti-tumor activity On-demand release of drug	(Chai et al., 2020)
Gold nanorods	Redox-responsive	Breast cancer	214–433 nm −22.7 to −27.2 nm 56.8%	Doxorubicin	Hyaluronic acid	Hyperthermia-related chemotherapy Reduced drug efflux Increased cellular uptake	(Li, Xu, et al., 2019)
Polymeric nanocomplex	Redox- and pH-dual responsive	Breast cancer	140–190 nm −15 mV	Doxorubicin	Hyaluronic acid	Mildly acidic pH or high GSH conditions induced DOX release High targetability Enhanced anti-tumor activity	(Lu, Xiao, et al., 2020)
Mesoporous silica nanoparticles	Redox- and pH-dual responsive	Cervical cancer	110 nm	Doxorubicin	Hyaluronic acid	Controlled release of cargo in reducing and acidic conditions High cellular uptake Inhibited cancer progression	(Lin et al., 2017)
Carbon dots	Redox- and enzyme-dual responsive	Lung cancer	230 nm −21.4 to +38.6 mV 30.5%	Doxorubicin	Hyaluronic acid	High biocompatibility and excellent fluorescence Enhanced cellular uptake in lung cancer cells through CD44-mediated endocytosis Dual-stimuli responsive with simultaneous imaging capability	(Zhao et al., 2017)
Mesoporous silica nanoparticles	Redox- and pH-dual responsive	Breast cancer	100 nm −25.3 mV	Doxorubicin	Hyaluronic acid	Apoptosis induction CD44-mediated endocytosis High cell targeting capability	(Lu, Xiao, et al., 2020)
Micelles	Redox- and pH-sensitive	Lung cancer	188.4 nm −17.54 mV	Doxorubicin	Hyaluronic acid	Rapid DOX release in reducing or low pH conditions Receptor-mediated endocytosis Apoptosis induction and high cytotoxicity against cancer cells	(Yin et al., 2018)
Carbon dot-nanogel	pH-sensitive	Ovarian cancer	20–43 nm 32.5%	Doxorubicin	Hyaluronic acid	Weakly acidic environment-induced DOX release Nuclear accumulation Receptor-mediated endocytosis	(Jia et al., 2016)
PEGylated nanoparticles	pH-sensitive	Breast cancer	30–50 nm	Doxorubicin	Hyaluronic acid	Increased circulation time by 12.5 fold Selective targeting of cancer cells High anti-tumor activity against cancer cells	(Zhang, Zhao, et al., 2020)
Mesoporous silica nanoparticles	pH-responsive	Cervical cancer	150 nm −28 mV 18.2%	Doxorubicin	Hyaluronic acid	Cancer cell internalization by binding to CD44 receptors Inhibited cancer growth Promoted DOX cytotoxicity against cancer cells	(Wang, Tian, et al., 2016)
Mesoporous silica nanoparticles	pH-responsive	Cervical cancer	186 nm −16.8 mV	Doxorubicin	Hyaluronic acid	High anti-tumor activity against cancer cells Increased internalization CD44-mediated endocytosis	(Chen, Sun, et al., 2018)
Polymeric nanoparticles	Light-responsive	Breast cancer	90–272 nm −3.62 to −5.89 mV Up to 82.6%	Doxorubicin	Hyaluronic acid	Provided deep penetration into tumors Well-tolerated Inhibited tumor growth Synergistic effect between photochemical internalization and doxorubicin	(Ji et al., 2019)
Gold nanoparticles	pH and NIR-responsive	Breast cancer	70.9 nm −11.4 mV	Doxorubicin	Hyaluronic acid	Provided simultaneous chemotherapy and photothermal therapy	(Xu et al., 2017)

(*continued on next page*)

Table 2 (*continued*)

Nanovehicle	Sensitive type	Cancer type	Particle size (nm) Zeta potential (mV) Encapsulation efficiency (%)	Drug or gene	Surface modification	Remarks	Refs
Mesoporous silica-coated gold nanorods	pH-, enzyme- and NIR sensitive	Ovarian cancer	50–124 nm −8 mV	Doxorubicin	Hyaluronic acid RGD peptide	Apoptosis induction High intracellular accumulation Long blood circulation time Increased efficacy of DOX in cancer chemotherapy plus photothermal therapy CD44 and integrin-mediated endocytosis in cancer cells	(Zhou et al., 2017)

potential biomedical applications in bioimaging, chemotherapy, photodynamic and photothermal therapy (Guo et al., 2018; Horcajada et al., 2010; Wu et al., 2018; Yao et al., 2019) as exemplified by MIL-100, a type of MOF, that has been utilized for drug delivery owing to its high drug loading capacity (Gupta et al., 2019). MIL-100 produced by microwave-assisted synthesis could be loaded with DOX. Further surface modification of the MOF nanoparticles with HA has been performed to provide tumor-targeted delivery. These nanoparticles could provide simultaneous chemotherapy and photodynamic therapy, leading to the increased anti-tumor activity of DOX (Xue et al., 2019). Superparamagnetic iron oxide nanoparticles (SPIONs) possess a variety of beneficial attributes, such as biocompatibility, large surface area and magnetic characteristics (Heydari Sheikh Hossein et al., 2020; Lee et al., 2015; Reddy et al., 2012; Zafar et al., 2014) and they can be directed towards target sites by the application of external magnetic fields (López-Viota et al., 2017). The agglomeration and clearance of SPIONs from the blood circulation can be reduced by appropriate surface modifications (Akbarzadeh et al., 2012; Muthiah et al., 2013; Patsula et al., 2019). Their modification with HA improved the biocompatibility while reducing the uptake by macrophages (Fang et al., 2019; Ting Gong et al., 2019). Furthermore, lipid/HA-coated DOX-Fe_3O_4 nanoparticles demonstrated a high cellular uptake by endocytosis (Curk et al., 2017; Gupta et al., 2018). In one study, lipid/HA-coated DOX-Fe_3O_4 nanoparticles were assessed in cancer therapy where these nanocarriers with an average size of 48.2 nm could easily be taken up into breast cancer cells through endocytosis. In vitro and in vivo studies demonstrated the high tumor-specificity of these nanocarriers and their capacity to suppress growth and viability (Liang et al., 2020). This enhanced cytotoxicity of DOX against cancer cells was due to the targeted delivery and enhanced cellular uptake provided by HA-based nanomaterials.

As mentioned earlier, one of the benefits of surface modification of inorganic materials with HA is avoiding uptake by macrophages which are key players in the tumor microenvironment and their presence with an anti-inflammatory M_2 phenotype increases the malignancy and survival of cancer cells (Mantovani et al., 2017; Qian & Pollard, 2010). It has been reported that surface modification of DOX-loaded Fe_3O_4 nanocarriers with HA enhanced their selectivity towards tumor-associated macrophages. The killing of M_2 macrophages increased the

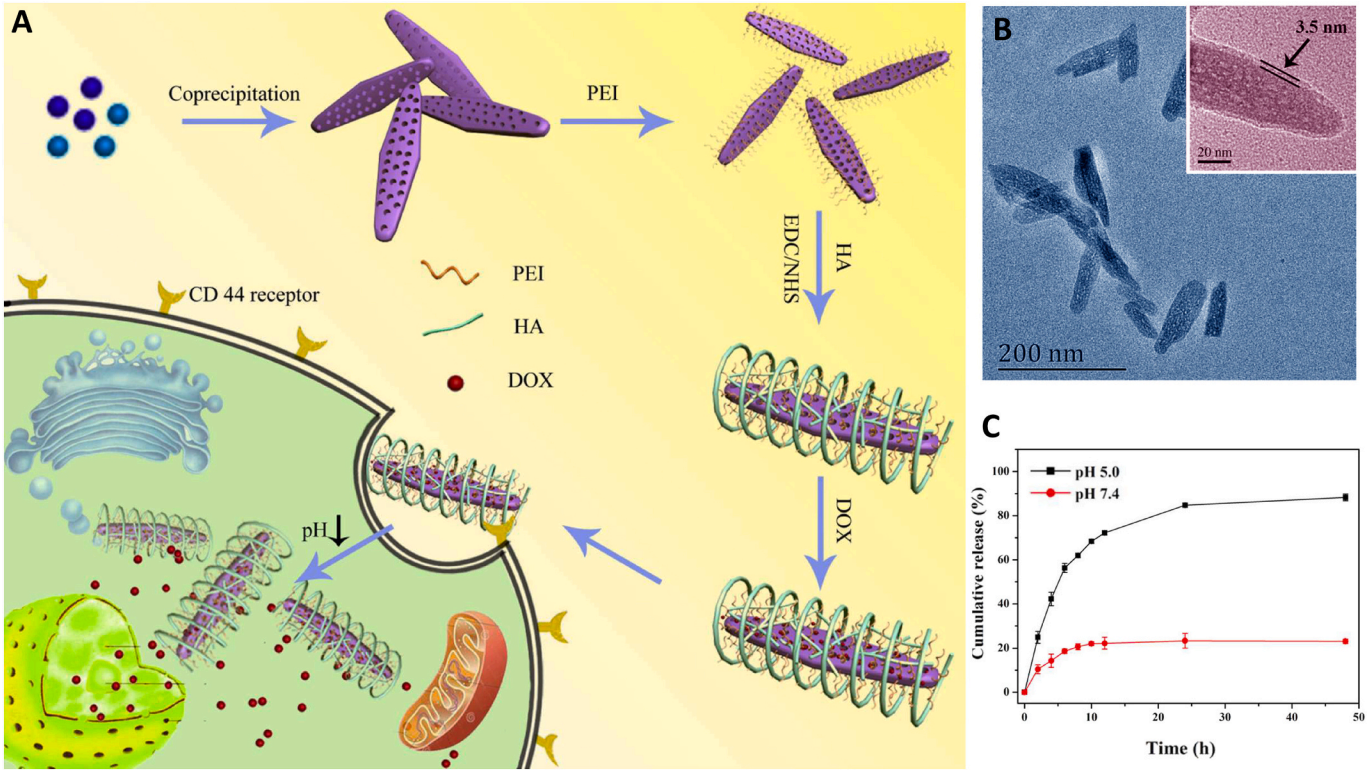

Fig. 4. Doxorubicin-encapsulated nanocarriers functionalized with hyaluronic acid. (A) Schematic of the preparation procedure. (B) TEM image of the particles. (C) Cumulative release profiles of doxorubicin from the nanocarriers under neutral and acidic conditions.
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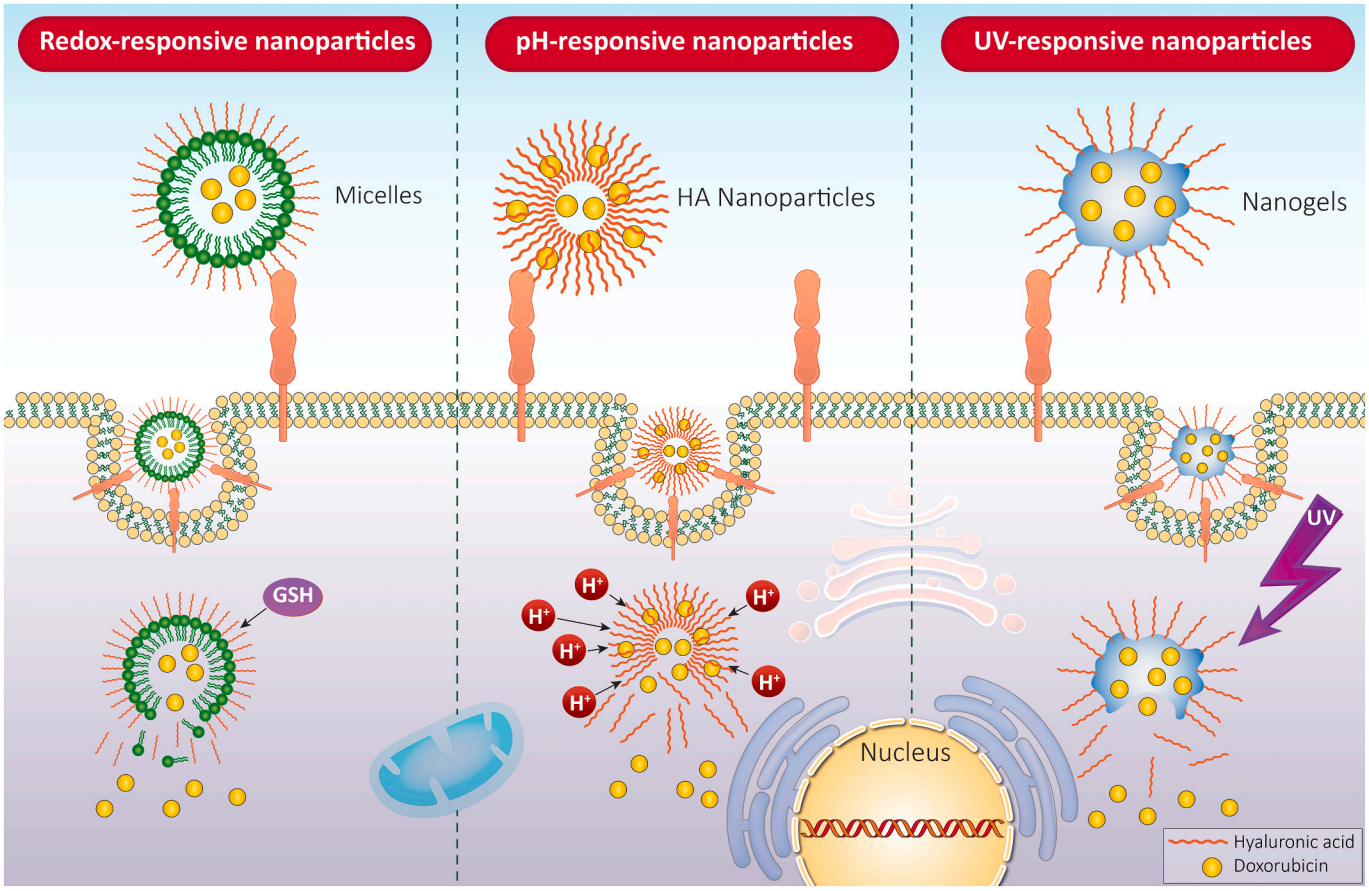


Fig. 5. Smart HA-based nanoarchitectures for DOX delivery in cancer therapy. These nanoparticles are taken up into cancer cells through endocytosis, leading to enhanced cellular uptake of DOX. Further modifications can provide stimulus-responsive release of DOX such as changes in GSH levels, pH values, and light activation. HA, hyaluronic acid; DOX, doxorubicin, GSH, glutathione.

proportion of anti-tumor M_1 polarized macrophages and promoted the anti-tumor immunity against breast cancer cells (Gong et al., 2019). HA-coated inorganic nanomaterials can improve the cytotoxicity of DOX against cancer cells and more studies are justified to realize their full potential (Cai et al., 2016).

4.4.2. *Stimuli-responsive inorganic nanoparticles*

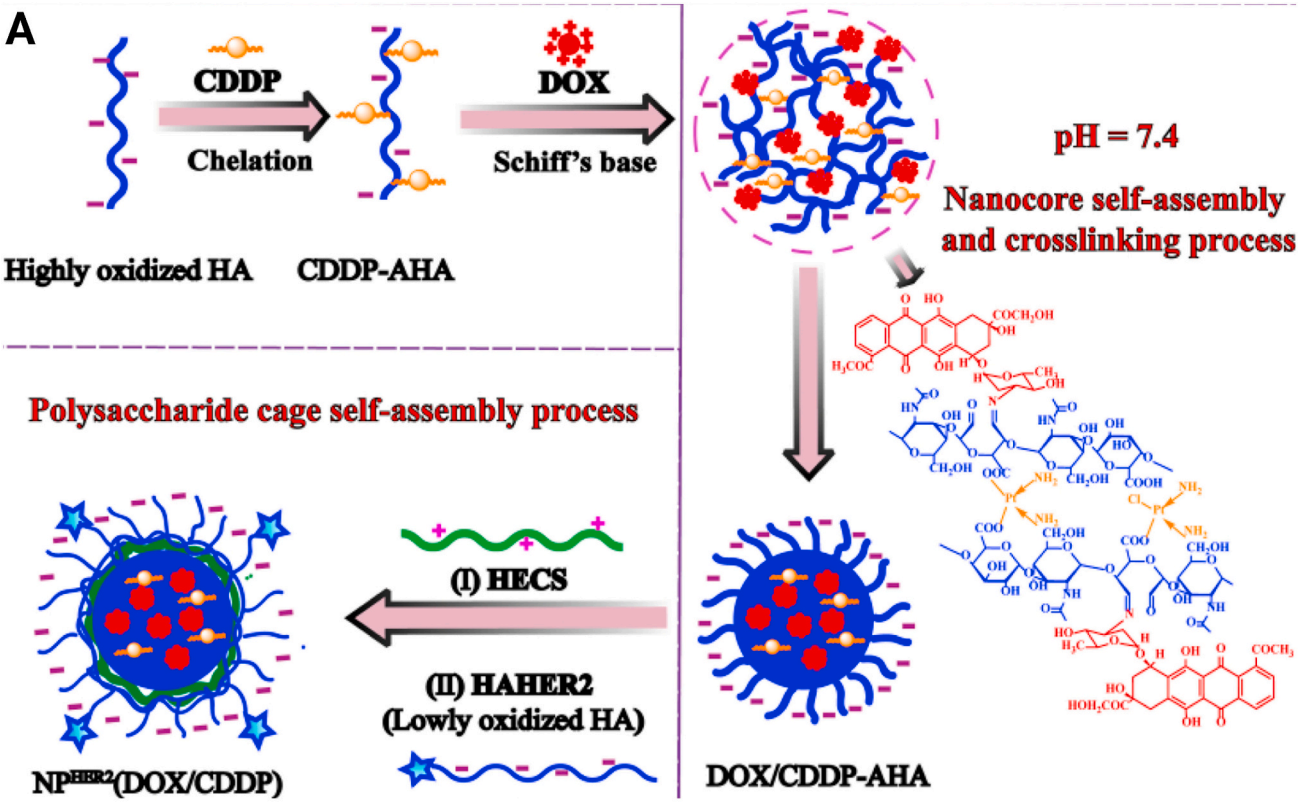
Light-induced hyperthermia is another promising strategy for enhancing the cytotoxicity and therapeutic efficacy of chemotherapeutic agents (Podolska et al., 2020). HA-gold nanorods were designed for DOX delivery. They were redox-responsive because of the cystamine use as a crosslinker and were degraded at high GSH concentrations. NIR light-induced hyperthermia, caused by energy absorption by the gold nanorods, suppressed the DOX resistance (Li, Xu, et al., 2019). Even though there are few potential strategies for DOX release, additional studies are required to extend the use of smart HA nanocarriers for DOX delivery in clinical settings (Table 2) (Alves et al., 2019; Debele et al., 2018; Hang et al., 2017; Hu et al., 2016; Hu et al., 2017; Jeong et al., 2019; Lee et al., 2020; Liao et al., 2018; Liu, Li, et al., 2020; Mao et al., 2019; Palanikumar et al., 2018; Poudel et al., 2020; Shin et al., 2019; Sun et al., 2019; Wu et al., 2019; Yang et al., 2017; Yu et al., 2020; Zhang et al., 2018). Fig. 5 illustrates the use of smart HA-based materials for DOX delivery in cancer treatment. The following key points can be concluded (Fig. 4):

A) Among different kinds of nanoparticles, a special attention has been directed towards surface modification of polymeric nanoparticles with HA for improving their characteristics,
B) In addition to polymeric nanoparticles, lipid-based nanocarriers, inorganic materials and carbon-based nanostructures have been modified by HA in increasing delivery of DOX to cancer cells (Poudel et al., 2020),
C) There is no study evaluating role of smart HA-modified carbon-based nanocarriers for DOX delivery and cancer treatment. In terms of capacity of CDs in bioimaging and their application as diagnostic factors, it would be beneficial to develop advanced HA-modified CDs for DOX delivery and simultaneously, trace response of cancer cells.

5. Hyaluronic acid for co-delivery of drugs or genes along with DOX

5.1. *Co-delivery of drugs and DOX*

Among the strategies to overcome DOX resistance, the combination of DOX with other anti-tumor compounds has prominence as they sensitize the cancer cells to chemotherapy (Guo et al., 2020; Halim et al., 2019; Sabzi et al., 2020; Varughese et al., 2019). However, the other anti-tumor compounds may still have their drawbacks. For instance, the use of anti-tumor drugs such as cisplatin (CP) eventually leads to the induction of resistance, and deployment of naturally occurring anti-tumor compounds, such as curcumin, quercetin or resveratrol, have limitations because of poor bioavailability (Algahtani et al., 2020; Hussain et al., 2021; Ma et al., 2020; Mirzaei, Hushmandi, et al., 2021). HA-based nanocarriers can provide a platform for the co-delivery of DOX along with other anti-tumor compounds for more effective cancer therapy. In this section, we provide a mechanistic discussion on the use of HA-based nanoscale delivery systems for DOX and other anti-tumor compounds.



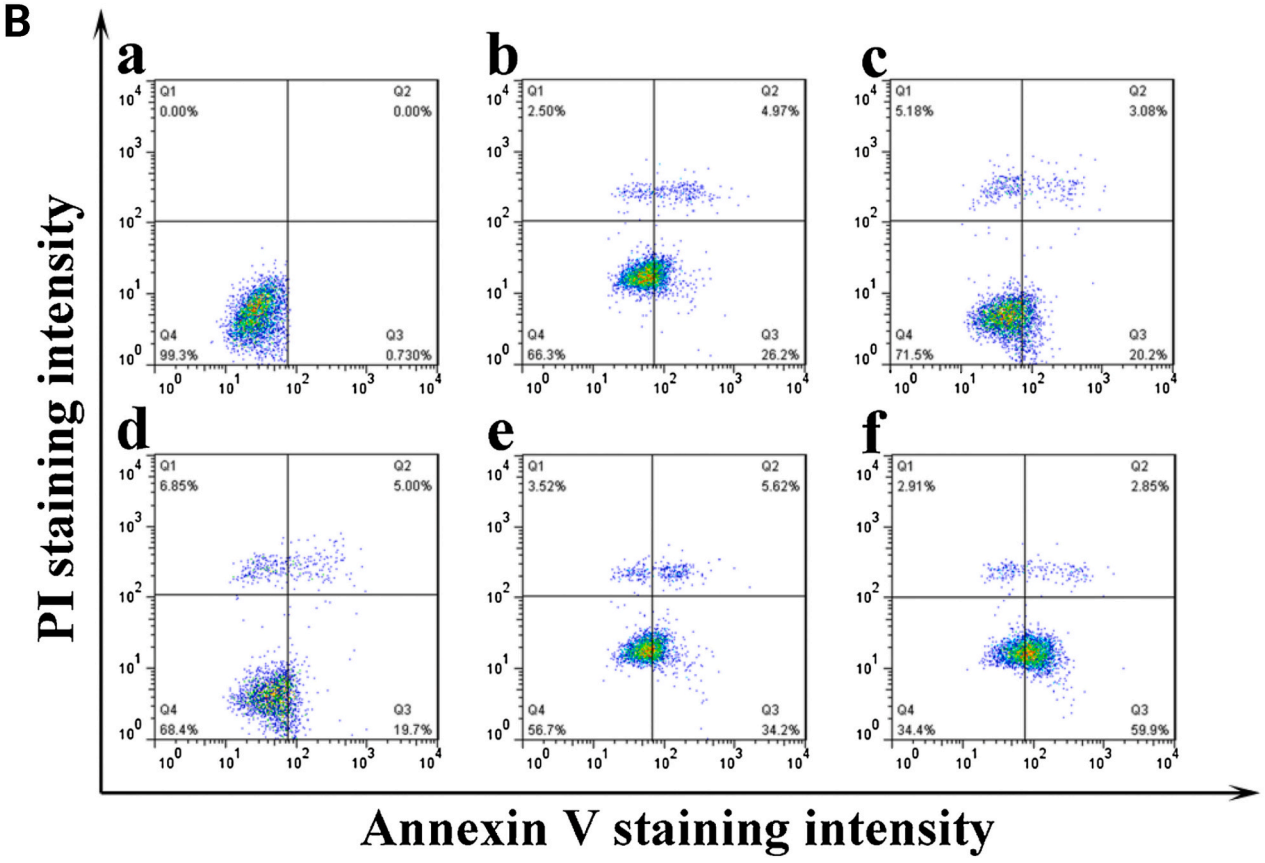


Fig. 6. (A) Preparation of HA-modified nanoparticles for co-delivery of DOX and CDDP; (B) Apoptotic effect of MCF-7 cells treated with PBS (a), free DOX (b), free CDDP (c), NP(DOX) (d), NPHER2(DOX) (e) and NPHER2(DOX/CDDP) (f). The lower left, lower right, upper right and upper left quadrants in each flow cytometric sorting profile present the percentages of living, early apoptotic, late apoptotic and necrotic cells, respectively.
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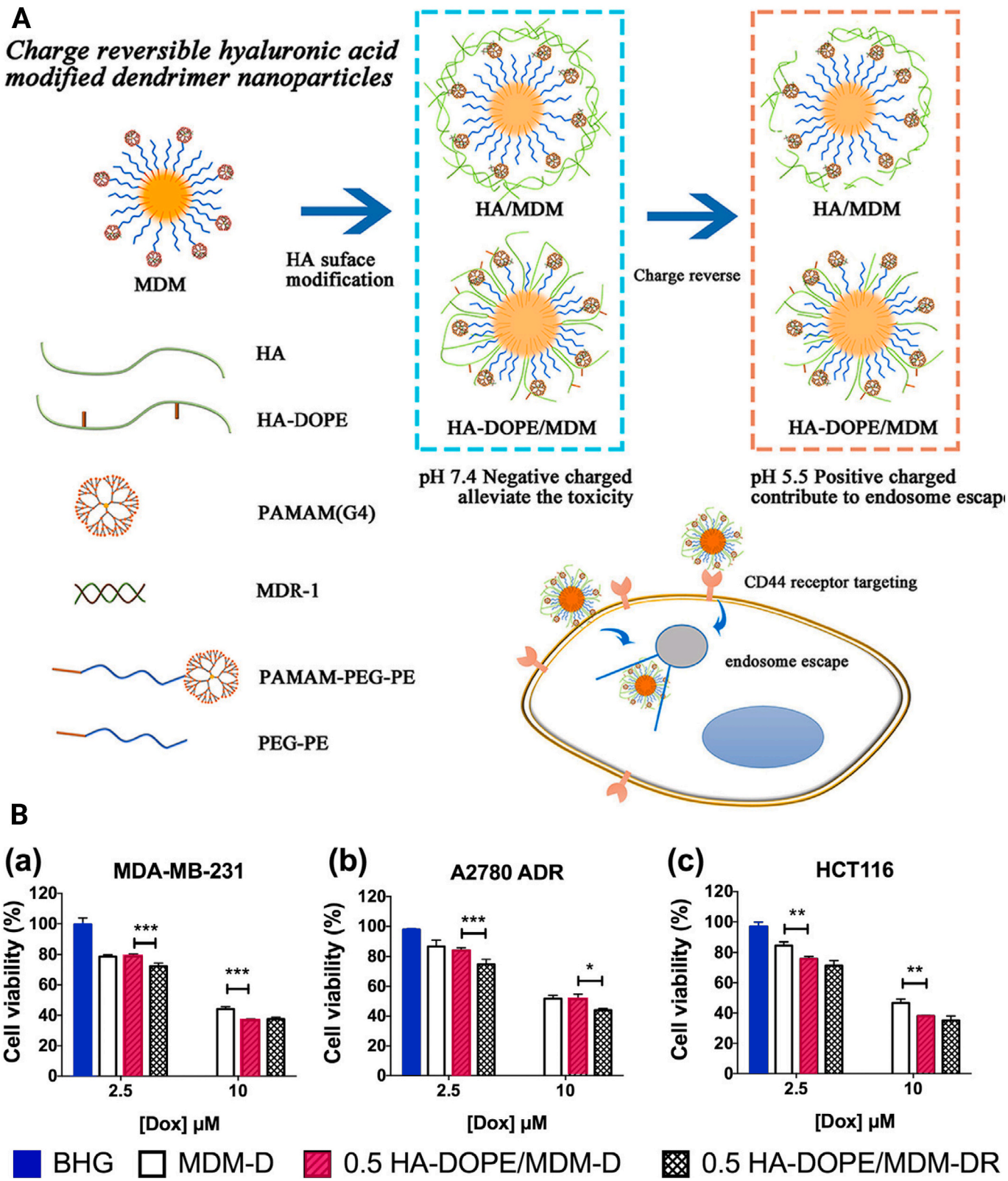

Fig. 7. (A) Preparation of charge reversible HA-modified dendrimer micelles; (B) Cytotoxicity of Dox-loaded MDM, HA-DOPE/MDM-loaded with Dox and HA-DOPE/MDM-loaded with Dox and 100 nM of siMDR-1 in (a) MDA-MB-231; (b) A2780 ADR; (c) HCT 116 cells compared with cells treated with BHG. Results indicate mean ± SD, $n = 3$. ***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.05$.
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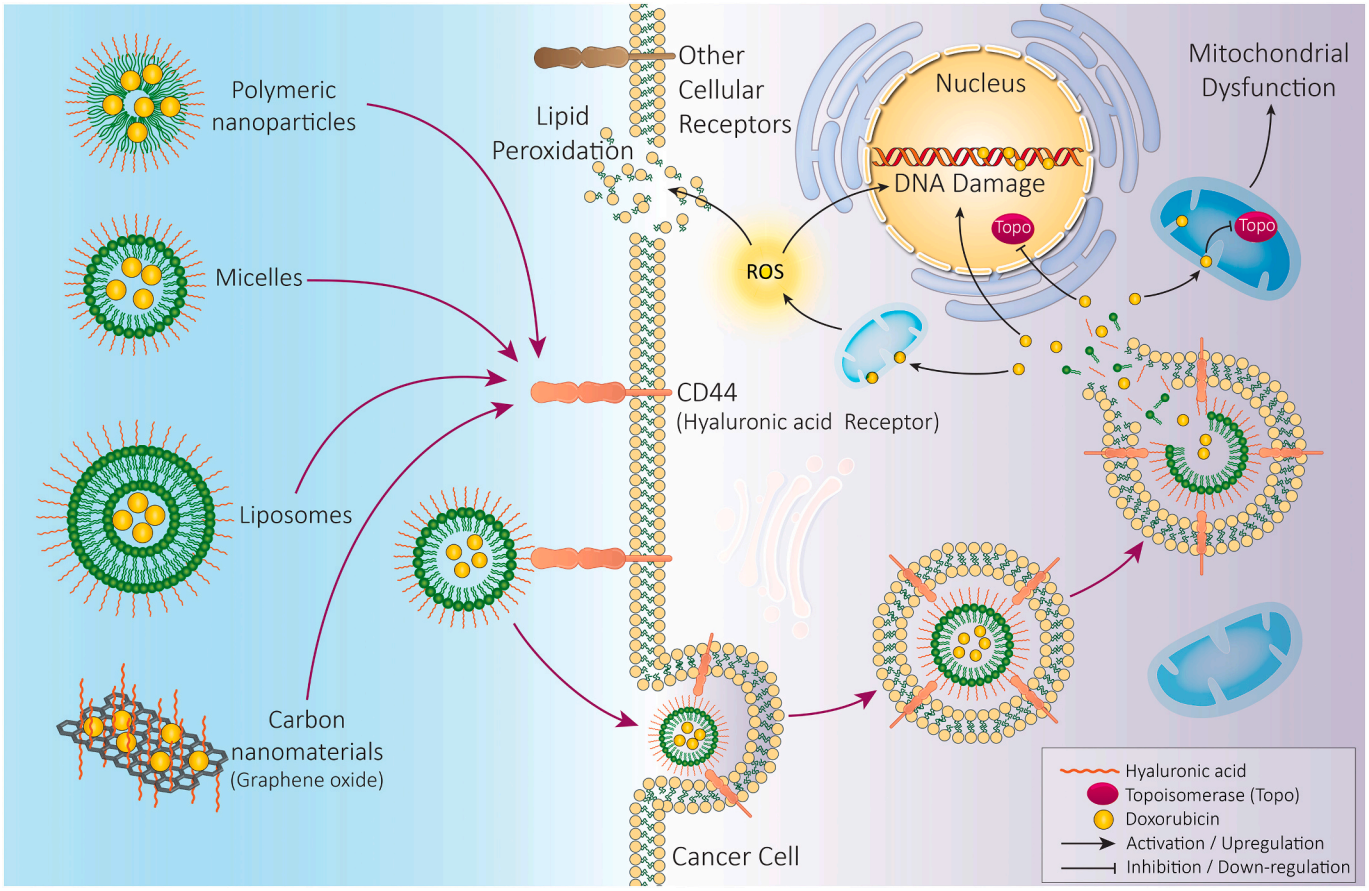

Fig. 8. HA-based nanovehicles increase cell uptake of DOX, induce cell death by increasing ROS levels, mediating mitochondrial dysfunction, and causing DNA damage. HA, hyaluronic acid; DOX, doxorubicin; ROS, reactive oxygen species.

CSCs play a significant role in cancer progression and metastasis, and therefore targeting of CSCs is the key in cancer eradication (Bhuvanalakshmi et al., 2018; Ma et al., 2019; Najafi et al., 2019). Anti-tumor compounds can be designed to be co-administered with DOX to target CSCs. Cyclopamine is a steroid alkaloid that acts as an inhibitor of CSCs and an amphiphilic nanocarrier was designed for the co-delivery of DOX and cyclopamine. The nanocarrier comprised hydrophobic PLGA as a head group and a hydrophilic HA segment connected by a bio-reducible disulfide bond. Because of the HA groups, these carriers could effectively target CD44 over-expressed on breast CSCs, and because of the bio-reducible linkage, they responded well to the redox environment. Compared to monotherapy, this combination remarkably reduced the size and spheroid formation of CSCs and inhibited the breast cancer growth as confirmed by in vitro and in vivo experiments (Hu et al., 2015). Various kinds of HA-based nanostructures can be synthesized for the delivery of DOX and other anti-tumor compounds. It has been reported that HA conjugates can be loaded with and release another anti-tumor compound apart from DOX. For instance, gemcitabine (GEM) was released faster than DOX and had a higher efficacy compared to other types of HA conjugates (Vogus et al., 2017).

Plant derived-natural compounds are also promising candidates for co-delivery with DOX due to their ability to target various molecular pathways responsible for cancer growth (Aziz et al., 2021; Chaitanya et al., 2021; Kashyap et al., 2019; Sethi et al., 2018; Shanmugam et al., 2017). Modification of lipid carriers with HA can promote their selectivity towards lung cancer cells. Loading DOX and baicalein on HA-modified lipid carriers promoted their cellular uptake and showed a synergistic effect between baicalein and DOX to effectively eradicate lung cancer cells (Liu et al., 2016). The same strategy was applied for the co-delivery of HA with quercetin or gallic acid, among other naturally occurring anti-tumor compounds. These compounds can increase the anti-tumor activity of DOX by inducing apoptosis and inhibiting tumor growth. HA-based nanocarriers can provide a platform for the co-delivery of DOX along with natural compounds and enhance their cellular uptake (Liu, Li, et al., 2020; Shao et al., 2019). Although these experiments have focused on augmenting anti-tumor activity of DOX, it is quite clear that combination cancer therapy with DOX and anti-tumor agents prevents development of drug resistance and the role of HA-modified nanoparticles is to provide a platform for their co-delivery. Overall, the use of HA-based nanomaterials enhanced the intracellular accumulation of DOX and the additional anti-tumor compounds, and provided the synergistic benefits that could be key in increasing the potential of DOX for cancer therapy and preventing the development of resistance (Fig. 6) (Lee et al., 2020).

5.2. *Co-delivery of genes along with DOX*

Another possibility to overcome DOX resistance is the deployment of nucleic acid genetic-based approaches wherein small interfering RNA (siRNA) and CRISPR/Cas9 systems have been utilized for down-regulating the genes that are involved in chemoresistance (Ashrafizadeh, Hushmandi, Hashemi, et al., 2020; Ashrafizadeh, Hushmandi, Rahmani Moghadam, et al., 2020; Li, Tan, et al., 2020; Xing & Meng, 2020). However, there is still room for improving the efficiency of genetic tools in cancer therapy. For instance, gene therapy suffers from several off-target effects and displays instability. Moreover, RNA-based approaches namely siRNA or microRNAs can be quickly degraded by RNase enzymes when circulating in the bloodstream (Mirzaei, Gholami, et al., 2021; Mirzaei, Mahabady, et al., 2021; Zhupanyn et al., 2020; Zou et al., 2020). Therefore, nanocarriers could be promising alternatives to

Table 3
HA-functionalized materials in the co-delivery of DOX with other anti-tumor compounds or nucleic acids.

Nanovehicle	Cancer type	Anti-tumor compound	Gene	Particle size (nm) Zeta potential (mV) Encapsulation efficiency	Remarks	Refs
HA-functionalized PAMAM dendrimer	Breast cancer	Doxorubicin	SiRNA-MVP	285 nm 2.3 mV	MVP down-regulation Increased potential of DOX in cancer chemotherapy Lengthened blood circulation High cellular uptake Enabled DOX to access the nucleus	(Han et al., 2012)
Magnetic polydopamine nanoparticles	Cervical cancer	Doxorubicin Methotrexate	–	236.5 nm −22.5 mV	Enabled simultaneous chemotherapy and photothermal therapy Selectivity towards cancer cells due to surface modification by HA Enhancing DOX accumulation in cancer cells	(Li et al., 2018)
Polymeric nanoparticles	Lung and cervical cancer	Doxorubicin Methotrexate	–	200 nm −23.97 mV	Theranostics and image-guided delivery Increased cellular uptake Deep tumor penetration Uptake by endocytosis Combined chemotherapy and photothermal therapy	(Chen, Chen, et al., 2019)
Polymeric nanoparticles	Triple-negative breast cancer	Doxorubicin Gemcitabine	–	–	Suppressed aggressive and malignant behavior Inhibited tumor growth in vivo after intravenous and subcutaneous injection	(Vogus et al., 2017)
Polymeric nanoparticles	Breast cancer	Doxorubicin Cisplatin	–	160 nm −28 mV	HER2-mediated cellular uptake Synergistic anti-cancer effects between DOX and cisplatin	(Varughese et al., 2019)
Dendrimer nanoparticles	Different cancers	Doxorubicin	siRNA-MDR-1	225 nm −18 mV	HA coating shielded positive charge of PAMAM nanocarriers Enhanced cellular uptake Reduced cytotoxicity against normal cells High stability Synergistic effects in suppressing cancer progression	(Zhang, Pan, et al., 2020)
Lipid nanoparticles	Breast cancer	Doxorubicin Baicalein	–	103.5 nm +12.6 mV 90.8% (baicalein) 91.5% (DOX)	Exerted synergistic effects Suppressed cancer growth and viability	(Liu et al., 2016)

increase the efficacy of gene therapy (Delfi et al., 2021). In this section, some HA-based nanoparticles that have been developed for the co-delivery of DOX along with other nucleic acid-based tools, are discussed.

MicroRNAs (miRNAs) are endogenous, short single-stranded RNA molecules with a length of 19–24 nucleotides (Ashrafizadeh, Ang, Moghadam, et al., 2020; Ashrafizadeh, Hushmandi, Hashemi, et al., 2020; Ashrafizadeh, Hushmandi, Rahmani Moghadam, et al., 2020; Welponer et al., 2020). MiRNA dysregulation often occurs in cancer cells, and the expression of many tumor-suppressor miRNAs is lower, thus encouraging cancer progression (Hong et al., 2020; Mirzaei, Zarrabi, et al., 2021). One potential strategy is to supplant the low expressed miRNAs by delivering them using nanoparticles. HA-coated PEI-PLGA nanostructures were developed for the co-delivery of DOX and miRNA-542-3p to treat triple-negative breast cancer. In addition to suitable particle size (131.7 nm), the nanoparticles demonstrated high drug encapsulation efficiency (DOX) and inhibited the degradation of miRNA in serum. MDA-MB-231 cells expressing high levels of CD44 were targeted by the HA-coated nanoparticles. Both, the DOX and miRNA-542-3p were internalized and inhibited the breast cancer cells by triggering apoptosis, up-regulation of p53 and down-regulation of survivin (Wang, Zhang, et al., 2016). Compared to lipofectamine applied for miRNA transfection, HA-modified nanoparticles demonstrate more capacity in enhancing expression level. However, it should be noted that high expression level of miRNA may be toxic for normal cells. Therefore, a rational increase should be made in miRNA expression (Fu, Peng, et al., 2019).

SiRNA can reduce the expression of target genes, leading to down-regulation of the expression of tumor-promoting proteins, and suppressing the cancer progression (Akbaba et al., 2020; Ashrafizade et al., 2021; Ashrafizadeh, Zarrabi, Hushmandi, et al., 2020). SiRNAs are also a potential tool to improve the chemosensitivity in cancer cells (Joshi et al., 2020). Recently, HA-based dendrimeric nanocarriers were prepared for the co-delivery of DOX along with siRNA-MDR-1. HA was used to coat the nanocarriers to shield the positive charges and promote the selectivity towards cancer cells overexpressing CD44. Additionally, the HA-based nanoparticles protected the siRNA against RNase-mediated degradation and increased its stability. Because the HA coating shielded the positive charges, the biocompatibility improved significantly. The high specificity and cellular uptake of DOX and siRNA led to effective cancer treatment and reduced drug resistance (Table 3, Fig. 7) (Zhang, Pan, et al., 2020). These studies showed that HA not only could improve the targeting and specificity of the nanoparticles but also protected the nucleic acids against degradation in vivo. This makes them suitable for further investigations in clinical settings. Fig. 8 provides an overview of the anti-cancer activity of HA-coated DOX-loaded nanocarriers.

6. Theranostic applications

HA-based nanoparticles can be utilized as theranostic agents in cancer therapy, providing simultaneous imaging and drug delivery. Recently, a conjugate of DOX-HA-methotrexate (MTX) was prepared as a prodrug for theranostic applications where DOX-MTX was attached to the HA backbone. To provide image-guided delivery, indocyanine green was used for fluorescence imaging. These nanocarriers had a variety of advantages including suitable particle size (200 nm), high physiological stability and effective photothermal capability. Due to the EPR-mediated tumor accumulation, and uptake into cancer cells through

CD44-mediated endocytosis, the DOX-MTX-HA displayed a higher accumulation at the tumor site. HA-based nanocarriers induced apoptosis and inhibited tumor growth as NIR irradiation caused an increase in temperature and the resulting hyperthermia increased the efficacy of chemotherapy (Chen, Chen, et al., 2019). Theranostic applications of HA-based nanocarriers can be achieved by incorporating an imaging agent. Modification of graphene with HA and rhodamine B isothiocyanate (RBITC) produced dual-functional nanocarriers capable of targeted delivery of DOX and offered simultaneous imaging. DOX was loaded into the surface of HA/RBITC-graphene nanomaterials through π-π stacking, and as the fluorescence emission of the nanocarriers was quenched after DOX release, the fluorescence of the nanocarriers was recovered thus allowing imaging to be carried out; modification by HA enabled higher cellular uptake of DOX in cancer cells (Luo et al., 2016). As mentioned above, these HA-based theranostic agents can be activated by light, leading to simultaneous chemotherapy (DOX) and photothermal therapy (Khatun et al., 2015). As minimally invasive imaging and therapy are of importance in clinic for treatment of cancer patients, more experiments are required to reveal true potential of DOX-loaded HA-modified nanocarriers as theranostic.

7. Conclusions and remarks

In the present review, we have discussed the applications of HA-based nanoparticles as promising agents for the delivery of DOX to improve cancer chemotherapy. HA can enhance the targeted delivery of nanocarriers by allowing CD44-mediated endocytosis and subsequently, increase the DOX uptake into cancer cells. HA nanomaterials could solve some challenges faced in DOX chemotherapy by overcoming drug resistance and reducing the side effects. Lipid, polymeric, carbon-based, and metal nanoparticles have been modified with HA to increase the intracellular accumulation of DOX in cancer cells. As HA is a naturally occurring compound, the use of this polysaccharide to coat nanoparticles increases their biocompatibility that is of importance for further clinical application. Smart HA-based delivery systems can be designed to be responsive to internal stimuli such as pH or redox and to external stimuli such as NIR or UV radiation. Smart nanocarriers take advantage of distinct properties of the tumor microenvironment, such as mild acidic pH or high GSH concentrations to release DOX at the tumor site and promoting its cellular uptake. Additionally, light-responsive HA nanoarchitectures can enhance the potential of DOX in cancer chemotherapy by mediating photothermal therapy, a strategy that is also beneficial in preventing DOX resistance in cancer cells.

To increase the efficiency of DOX in cancer therapy, it can be combined with other anti-tumor compounds or various nucleic acid-based types of gene therapy. The ideal pathway to perform these kinds of combination therapies is to load both components into a single nanocarrier. HA-based delivery systems can provide a platform for the co-delivery of drugs or genes combined with DOX. Gene therapy with siRNA or miRNA can up-regulate tumor-suppressing factors or down-regulate tumor-promoting factors, thereby increasing the sensitivity of cancer cells to DOX. Not only can HA nanoparticles mediate the targeted delivery of nucleic acids, but they can also protect them against degradation in the biological environments. A newly emerging application of HA nanoparticles is in theranostics, allowing simultaneous imaging and therapy. When HA nanomaterials are used as theranostic agents, fluorescent dyes such as indocyanine green or RBITC are utilized to enable image-guided delivery of DOX to the tumors.

Although we have described the potential role of DOX-loaded HA nanoparticles in cancer therapy, the experiments described so far have been limited to pre-clinical studies (in vitro and in vivo). Because of the high biocompatibility of HA nanoparticles, further efforts should be made for their large-scale optimization, production, quality control, and testing in cancer patients to promote the efficacy of DOX in chemotherapy. Another limitation that can be explored is related to large-scale production of HA-modified nanoparticles for DOX delivery that requires an efficient method.

Declaration of competing interest

The authors declare no conflict of interest.

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