Materials Today Chemistry 4 (2017) 26–39

Contents lists available at ScienceDirect

Materials Today Chemistry

journal homepage: www.journals.elsevier.com/materials-today-chemistry/

Small molecule nanodrugs for cancer therapy

Yuan Ma [1], Quanbing Mou [1], Xinyuan Zhu*, Deyue Yan**

School of Chemistry and Chemical Engineering, State Key Laboratory of Metal Matrix Composites, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, PR China

ARTICLE INFO

Article history:
Received 8 December 2016
Accepted 5 January 2017
Available online 21 February 2017

Keywords:
Small molecule nanodrugs
Drug delivery
Cancer therapy

ABSTRACT

Nanoscale drug delivery systems (DDSs) have emerged as promising candidates for cancer therapy. However, traditional nanoscale DDSs suffer from several inherent drawbacks, including sophisticated synthesis, uncontrolled structure, low drug loading capacity, high reticuloendothelial system (RES) accumulation, unpredicted metabolic mechanism, and so on. In order to solve these problems, nanodrugs self-assembled from small molecules containing anticancer drugs have received great attention in recent years. Different from traditional nanoscale DDSs, small molecule nanodrugs (SMNs) exhibit unique advantages, such as simple synthesis, defined structure, high drug loading capacity, excellent tumor accumulation and low-toxic metabolism pathway. Hence, with rational design, SMNs can achieve excellent cancer therapeutic efficacy as well as low side effects, extremely promising for the clinic translation. Up to now, significant progress has been made for the exploration of SMNs for cancer therapy. In this review, we briefly summarize the design and synthesis, biological properties, as well as their wide range of applications for cancer therapy.

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1. Introduction

Nowadays, cancer has become the leading cause of mortality all over the world [1]. Up to now, there are versatile ways to fight against cancer, including surgery, chemotherapy, biotherapy, phototherapy, radiotherapy, and so on. Among these therapeutic methods, chemotherapy is an indispensable choice for its high efficiency. However, conventional chemotherapy suffers from several limitations, such as rapid blood/renal clearance, low tumor accumulation, nonspecific cytotoxicity, adverse side effects and severe multidrug resistance (MDR) [2]. In the past decades, nanoscale drug delivery systems (DDSs) have attracted extensive attention due to their unique properties such as prolonged residence time in blood circulation, preferential tumor accumulation, reduced systematic toxicity, ability to reverse MDR and improved therapeutic index [2]. Generally, in the DDSs, anticancer drugs can be delivered by versatile nanoscale carriers, including micelles [3], liposomes [4], dendrimers [5], hyperbranched polymers [6], inorganic nanoparticles [7], and so on. However, only a few nanotherapeutics have been approved by the Food and Drug Administration (FDA), which is due to the following obstacles. One major bottleneck is that most current DDSs are inconsistent and multicomponent systems accomplished through sophisticated procedure, which make difficulties for their industrial manufacture and quality control. The nanoscale DDSs suffer from inherent drawback of low drug loading capacity, resulting in large amount of carriers used in cancer treatment [8]. The repeated administration of drug carriers may impose an extra burden to the body and cause severe side effects during their degradation, metabolism and excretion processes [8]. In addition, most nanocarriers severely accumulate in the reticuloendothelial system (RES), in which the hepatic processing and biliary excretion are relatively slow, leading to potential long-term toxicity [9]. These deficiencies explain the limited number of marketed nanoscale DDSs, despite of the numerous literature in this field. Therefore, there is an urgent demand to design novel nanoscale DDSs appealing for clinical translation.

As mentioned above, the essential requirements for DDSs include simple fabrication, defined structure, high drug loading ratio and efficient metabolism pathway. Recently, one promising strategy to satisfy all these requirements is to develop small molecule nanodrugs (SMNs). As an efficient way to construct SMNs, drugs can be utilized as assembly component linked with biocompatible small molecules as excipient, including oligomers [8], squalene [10], peptides [11], phospholipids [12], and so on.

* Corresponding author.
** Corresponding author.
E-mail addresses: xyzhu@sjtu.edu.cn (X. Zhu), dyyan@sjtu.edu.cn (D. Yan).
[1] Equal contribution.

http://dx.doi.org/10.1016/j.mtchem.2017.01.004
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These small molecule prodrugs can self-assemble and form one-component nanodrugs with controllable and distinct physicochemical properties. However, in these small molecule DDSs, redundant carriers without therapeutic efficacy are still indispensable and may even cause potential damage. In 2012, the researchers in Shanghai Jiao Tong University (China) developed a carrier-free SMN self-assembled from an amphiphilic drug-drug conjugate (ADDC) in CN and US patents [13,14]. The experimental data showed that the ADDC self-assembled into nanoparticles in water successfully. Hence, anticancer drugs could exhibit nanoscale characteristics by their amphiphilic conjugation without the help of nanovehicles. This approach offered extremely high drug loading ratio (100%) and excellent therapeutic effect [15]. Moreover, the strategy of ADDC can be facilely extended to multifunctional and intelligent DDS by introducing functional agents as assembly components such as targeting agents [16,17] and imaging agents [18].

To date, various types of SMNs have been widely employed for cancer therapy owing to their facile fabrication process and unique biological properties. Firstly, compared with traditional nanoscale DDSs, SMNs possess simple synthesis and defined structure, which facilitates to tackle the commercial and regulatory challenges. Secondly, these SMNs achieve high drug loading capacity and hence ease the extra burden of the body during therapy [16]. Thirdly, SMNs not only retain nanoscale advantages such as enhanced pharmacokinetics and tumor accumulation, but also undergo low-toxic metabolism pathway in the form of dissociated individual molecules [18]. Therefore, SMNs have become some of the most promising therapeutics and excellent candidates for cancer therapy. However, systematic review in this field has not yet been published.

In this Review article, we summarize recent research progress in the development of SMNs, including their design and synthesis, biological properties, as well as their wide range of applications for cancer therapy. This Review intends to illustrate the exciting achievements of SMNs for cancer therapeutic applications and we hope to inspire continued endeavors in this promising research area.

2. Design and synthesis

2.1. Fabrication strategy

In view of the types of building blocks, SMNs can be constructed by not only various biocompatible molecules (such as oligomers [8,19,20], peptides [11], lipids [21], phospholipids [4], essential metal ions [22]), but also diverse functional molecules (eg. anticancer drugs [15,23], targeting ligands [16,24], imaging agents [18,25]). These biocompatible and functional molecules can be integrated into excellent nanoplatforms for cancer therapy through different assembly mechanisms, such as amphiphile self-assembly and nanoprecipitation [10,26–31]. Among them, amphiphile self-assembly is the most commonly used strategy to produce SMNs.

Typically, anticancer drugs should first interact with an auxiliary segments through covalent or non-covalent interactions to fabricate amphiphilicity building blocks, which can form nanoassembly in aqueous solution due to the solvophobic effect [32]. In the case of covalent interaction, anticancer drugs can be conjugated with appropriate auxiliary segments (such as biocompatible and functional molecules) through responsive linkages. For instance, Yan and Zhu prepared an amphiphilic drug-drug conjugate (ADDC), which was synthesized from hydrophilic anticancer drug irinotecan (Ir) and hydrophobic anticancer drug chlorambucil (Cb) via a pH responsive hydrolysable ester linkage [15] (Fig. 1). This amphiphilic Ir-Cb conjugate could self-assemble into nanoparticles in aqueous solution and exhibit excellent anticancer activity both *in vitro* and *in vivo*.

On the other hand, amphiphilic building blocks can be fabricated by anticancer drugs interacting with auxiliary segments through non-covalent interactions, such as hydrogen bonding interaction [4], host-guest recognition [33–36], or electrostatic adsorption [37,38] and other intermolecular forces [39]. For instance, in 2015, Zhu and coworkers designed a self-delivery SMN through hydrogen bonding interaction between two anticancer drugs [40,41]. Hydrophobic anticancer drug raltitrexed (RT) and hydrophilic anticancer drug clofarabine (CA) could self-assemble into stable nanoparticles through molecular recognition of base analog in water, which promoted their cellular uptake and facilitated the tumor accumulation. After cellular internalization, the hydrogen bonding interaction between RT and CA was broken and subsequently accelerated the release of free drugs, resulting in excellent anticancer activity *in vitro* and *in vivo*. In another case, Shen and coworkers prepared excipient-free nanodispersions using anti-tumor drugs, which was composed of hydrophilic irinotecan hydrochloride (CPT11) assembling with another hydrophobic drug 7-ethyl-10-hydroxy camptothecin (SN38) via π-π stacking interaction. These nanodispersions greatly increased the bioavailability and improved the anticancer activities of drugs. As mentioned above, SMNs composing of various biocompatible molecules with different biofunctions can be fabricated via diverse strategies.

2.2. Morphologies

In recent years, the self-assembly of small molecular drugs has experienced a rapid development and numerous delicate SMNs with various morphologies have been reported, such as spherical micelles [11,42], nano-vesicles [36,43,44], nanofibers [45,46], nanotubes [47,48], and so on [10,49,50] (Fig. 2). For instance, as reported by Zhu and coworkers, Ir-DOX conjugate fabricated from hydrophilic Ir and hydrophobic DOX can self-assemble into micelles in aqueous medium [3]. In addition, small molecule drugs can also self-assemble into nano-vesicles with narrow size distribution. For instance, Zhu, Wang and coworkers prepared a supramolecularly engineered phospholipid, which self-assembled into liposome-like bilayer structures in water and exhibited fast stimuli-responsive ability due to its hydrogen bonding connection [4]. Moreover, fibrillar nano-architectures can be obtained through rational molecular design. For example, Zhang and coworkers synthesized a prodrug $C_{13}H_{27}$-CONH-Arg-Gly-Asp-Ser-Lys(camptothecin) (camptothecin, CPT), which could self-assemble into nanofibers via hydrophobic interaction from alkyl groups, hydrogen bonding from peptide backbones and π-π stacking from quinoline rings of CPT [45]. What's more, various nanotubes can be fabricated by different small molecule drugs. As reported by Parquette and coworkers, both of CPT-lysine conjugate and CPT-dipeptide conjugate could self-assemble into well-defined nanotubes [47,48].

Small molecular drugs can self-assemble into topological structures with tunable and changeable morphologies. For instance, Stupp and coworkers developed a pH-sensitive self-assembly system based on peptide amphiphiles (PAs) to both control nanostructure shape and respond to the acidic tumor microenvironment [51]. As is well known, the morphology of PA assembly can be tuned through rational molecular design, including the choice of lipid tail along with the property of amino acids and their sequences in the β-sheet domain. According to this principle, they designed two PAs, which self-assembled into distinct morphologies (either as nanofibers or spherical micelles) by incorporating an oligo-histidine H_6 sequence with aliphatic tail on the N- or C-terminus, respectively. These cylinder and sphere-forming PAs could

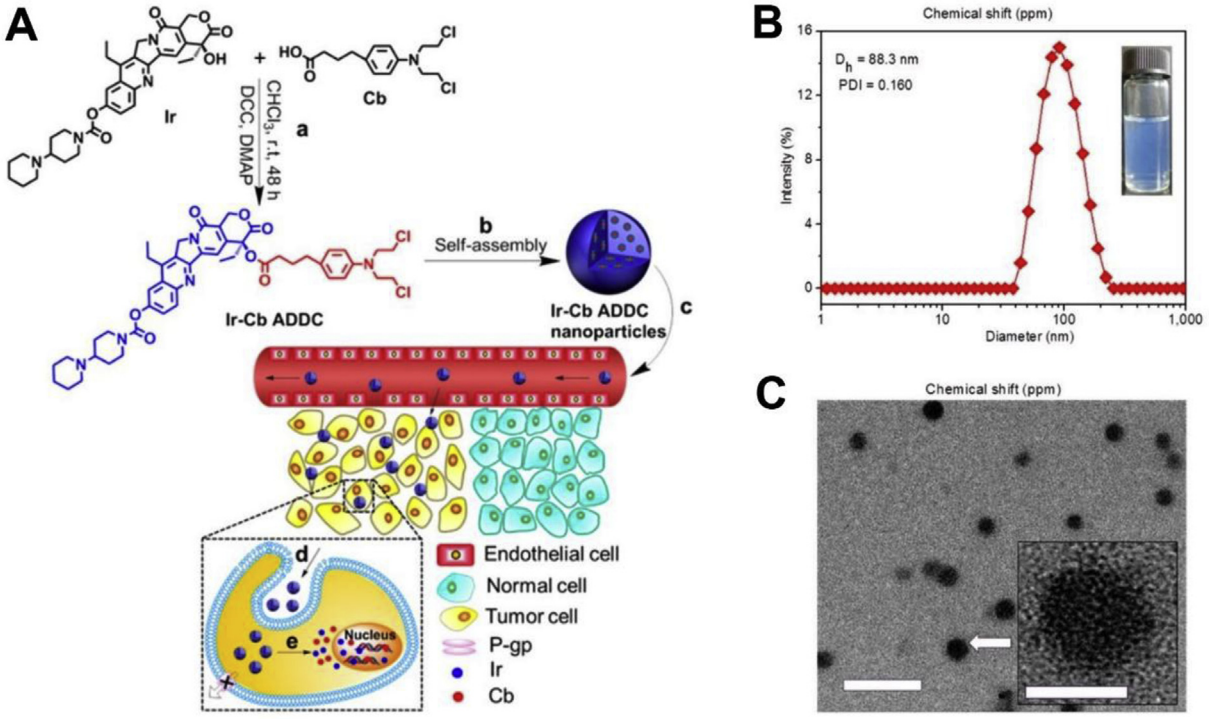

Fig. 1. SMN self-assembled from Ir-Cb ADDC for cancer therapy. (A) Schematic diagram of ADDC from fabrication, self-assembly to self-delivery. (B) DLS curve and a digital photograph of Ir-Cb ADDC nanoparticle solution. (C) TEM image of Ir-Cb ADDC nanoparticles. Scale bars: 200 nm (C), 50 nm (inset). Adapted with permission.[15] Copyright 2014, American Chemical Society.

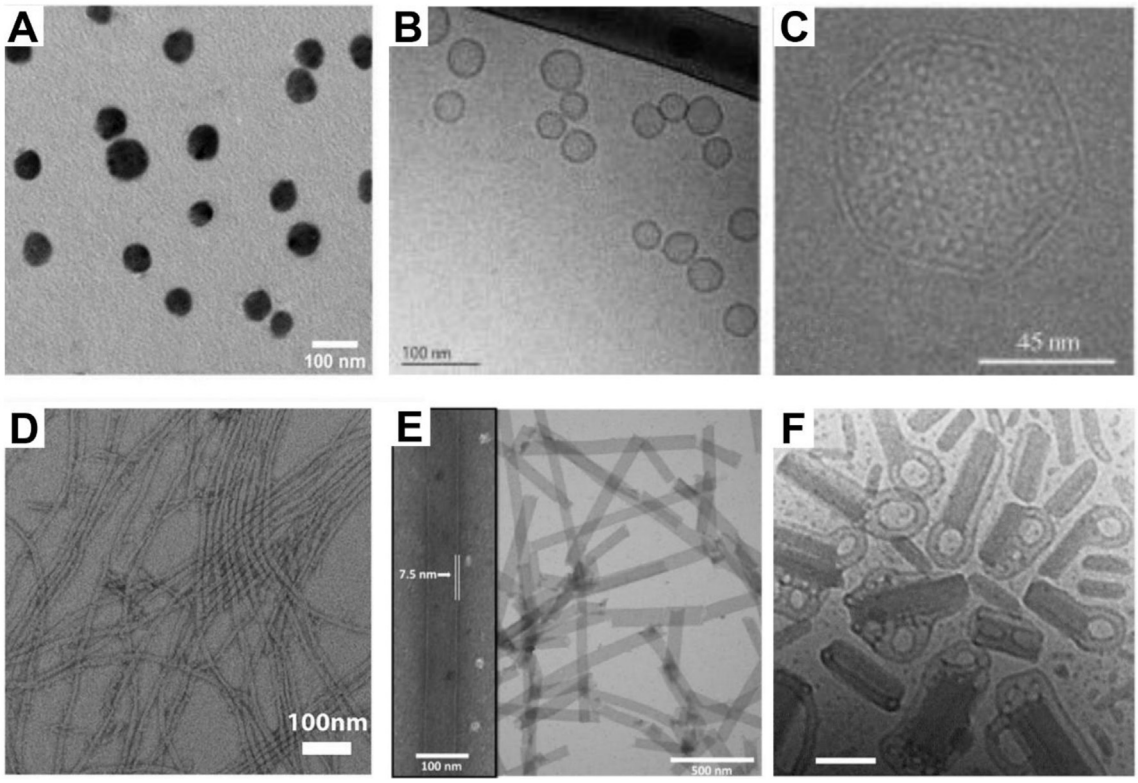

Fig. 2. Various self-assembled structures of versatile SMNs: (A) spherical micelles [42], (B) nano-vesicles [44], (C) hexagonal shape [50], (D) nanofibers [46], (E) nanotubes [47], (F) "loop-train" structure [10].

encapsulate CPT and underwent morphological transitions in an acidic environment to release free CPT. The pH-sensitive nanostructures showed high drug encapsulation, responsive drug release and excellent tumor accumulation *in vivo*.

2.3. Drug loading

In recent years, SMNs are emerging as potential DDSs because of their defined structure and tailored properties. Hence, the use of small molecule nanoparticles as drug carriers has been widely explored, which can deliver drugs via different mechanisms, such as encapsulation [52] and conjugation [53–57].

Typically, with rational design, small molecules can self-assemble into spherical micelles [11] and nano-vesicles [36,43], which may be capable of encapsulating anticancer drugs into the void spaces in the interior of nanoparticles. For example, Zhu and coworkers designed a supramolecularly engineered phospholipids based on complementary hydrogen bonding of nucleosides, which self-assembled into liposome-like bilayer structures in water to encapsulated anticancer drug DOX [4] (Fig. 3). These DOX-loaded supramolecular liposomes could effectively transport drugs into tumor site, enhance cellular internalization and release drugs quickly in response to intracellular acidic environment, resulting in excellent anticancer efficacy.

Although the strategy of drug encapsulation has been proved successfully, some limitations still exist, such as undesired drug leakage during blood systemic circulation and rapid drug release in the disease site. Fortunately, the appearance of the covalently bound drug conjugate solves these two problems, which can be reasonably designed to remain stable in the blood and responsively release drugs in the tumor. Hence, numerous and significant researches have focused on novel covalent drug attachment. Generally, the responsive linkages for covalent drug-conjugate have great impact on the controlled drug release property, which typically involve esterase cleavable ester groups, redox-responsive disulfide groups and acid-labile acylhydrazone groups and so on. One advantage of these small molecule drug conjugates is their defined and simple structure, which facilitates tackling the commercial and regulatory challenges. For instance, Cui and coworkers reported the design of monodisperse and defined amphiphilic anticancer drugs that could spontaneously associate into discrete and stable supramolecular nanostructure. This drug amphiphile was composed of CPT conjugated with β-sheet-forming peptide through the reducible disulfylbutyrate (bu**SS**) linker [58]. Thanks to the defined structure of small molecule drug conjugate, the drug content was precisely controlled and fine-tunable. Another advantage is that the drug loading ratios of small molecule drug conjugates can be extremely high, even reaching up to 100%. For example, Yan, Zhu and coworkers put forward a general concept of ADDC and tested a series of small molecule ADDC composed of two hydrophilic and hydrophobic anticancer drugs, such as Ir conjugated with Cb [15], floxuridine (FdU) conjugated with bendamustine (BdM) [59], DOX conjugated with Ir [3], Ir conjugated with BdM [60], gemcitabine (Gem) conjugated with Ir [61], CPT conjugated with FdU [62], methotrexate (MTX) conjugated with Gem [23]. These amphiphilic ADDC can self-assemble into nanoparticles and exhibit nanoscale characteristics by themselves without the help of nanovehicles, thus achieving 100% drug loading ratios. For the above-mentioned features, small molecule drug conjugates may open a new way for chemotherapy in cancer therapy and are hopeful for the treatment of cancer in clinic.

3. Biological properties

3.1. Stimuli-responsiveness

The clinical therapeutic efficacy of nanodrugs is highly determined by their on-demand responsive properties to release cargoes in the tumor site. With elaborate design, SMNs can be endowed with stimuli-responsive properties to tailor their release behaviors and enhance their therapeutic efficacy. These sensitive nanodrugs can change their morphology [51], self-assembly behavior [36] and

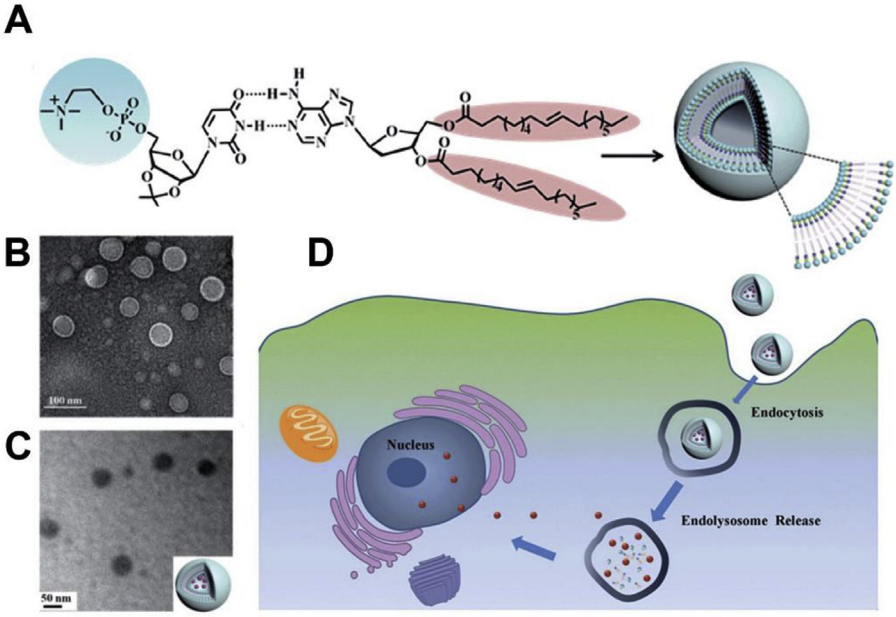

Fig. 3. Supramolecularly engineered phospholipids encapsulating anticancer drug DOX for cancer therapy. (A) Schematic representation of supramolecular liposome based on complementary hydrogen bonding of nucleosides. (B) Representative TEM image of negatively stained supramolecular liposomes. (C) Representative TEM image of DOX-loaded supramolecular liposomes. (D) Schematic representation for proposed mechanism of cellular uptake of supramolecular liposomes and intracellular drug release. Adapted with permission.[4] Copyright 2015, Royal Society of Chemistry.

chemical composition [45] to trigger drug release with respect to the corresponding environmental stimuli. Owing to the differentiated pathological environments in tumor, various internal stimuli can be utilized to stimulate drug release, including extracellular pH [63], redox agent [58,64] and enzyme [18] (Table 1). What's more, external stimuli, such as temperature [65] and photo [66] can also be used to achieve responsiveness for SMNs (Table 1).

Various pH-responsive SMNs have received much attention in recent years due to the wide presence of pH variations within the normal and pathophysiological states in the body. For example, the pH value in blood and normal tissues is around 7.4, while the extracellular pH in tumor tissues is slightly more acidic (pH = 6.5–7.2) [75]. In addition, various pH gradients also exist in the intracellular compartments of tumor cells, such as cytosol (pH = 7.4), endosome (pH = 5.0–6.5), lysosome (pH = 4.5–5.0) [76]. Hence, these mildly acidic environment can be utilized as triggers to assist pH-sensitive SMN to achieve the programmable and controlled drug delivery. Up to now, large numbers of pH-responsive SMNs have been designed and applied, which is mainly fabricated via three approaches: introducing acid-labile linkages [63], incorporating “titratable” groups [51], utilizing non-covalent interaction [4]. As the most widely used strategy, introducing pH-labile linkages into SMNs endows them with responsive property to release drugs at the determined site. Typically, these linkages involve acylhydrazone [16], ester [18], benzoic imine [70], carbamate [3] and so on. For example, Zhang and coworkers prepared a bioinspired nano-prodrug (BiNp) assembled by peptide-drug conjugate (FA-KLA-Hy-DOX), composed of folate acid (FA)-incorporated proapoptotic peptide $(KLAKLAK)_2$ (KLA) and anticancer drug DOX linked with hydrozone bond (Hy) [68]. Upon triggered by the intracellular acidic microenvironment of endosomes, DOX was released simultaneously to induce tumor cell apoptosis. In the same time, FA-KLA was also liberated to promote dysfunction of mitochondria and evoke apoptosis. *In vitro* and *in vivo* experiments demonstrated that BiNp exhibited programmed function to ensure the excellent therapeutic efficacy. Moreover, incorporation of “titratable” groups such as histidine into SMN is another strategy to introduce ideal pH sensitivity. For instance, Stupp and coworkers reported peptide amphiphiles (PAs) incorporating an oligo-histidine H_6 sequence, which could self-assemble into different nanomorphologies [51]. These PAs nanostructure exhibited reversible disassembly between pH 6.0 and 6.5 upon protonation of histidine residues in acidic environments. They used pH-sensitive PA assemblies to encapsulate hydrophobic anticancer drug CPT, and found that the morphological transitions induced by pH change could affect the drug encapsulation and tumor accumulation. In addition, several types of non-covalent interactions, such as hydrogen-bonding [4] and host-gest [33], have been used to create pH-sensitive SMNs. For example, Wang and coworkers designed a pH-responsive host-guest inclusion complex between hydrophilic pillar [6]arene and hydrophobic ferrocene derivative [36]. This inclusion complex could display a significant pH-responsive self-assembly behavior in water to encapsulate or release mitoxantrone (MTZ) in a controllable manner.

Various redox-sensitive SMNs are emerging as one of the most studied stimuli-responsive nanoscale DDSs in recent years [43,58,77]. Intracellular oxidation-reduction states are common in living organisms, owing to the difference in redox potential between oxidizing extracellular environment and reducing intracellular milieu. For instance, glutathione (GSH) is well known as the reducing agent in blood plasma and cellular cytosol with different concentration gradients. Generally, the concentration of GSH in blood plasma is micromolar, whereas its concentration in cytosol of normal cells is around 10 mM, several times lower than the level in tumor cells [78]. Since disulfide bond can be cleaved by GSH, disulfide-contained SMNs can be selectively triggered to release drugs in the cytosol of tumor cells. On the other hand, some cancer cells also have oxidizing intracellular milieu resulting from reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), hydroxyl radicals, and superoxide anions [64]. Hence, some redox-responsive SMNs act as intelligent drug delivery platforms. For example, Gu and coworkers proposed a SMN responding to both intracellular GSH and ROS to release anticancer drug [64]. These nanodrugs can release SN38 via thiolysis due to the intracellular GSH or hydrolysis in the presence of ROS. Hence, these nanodrugs possess high *in vitro* anticancer cytotoxicity and *in vivo* therapeutic activity.

Apart from the pH and redox, other internal and external stimuli have also been used to trigger drug release for responsive SMNs, such as enzyme [8,62], temperature [65,73] and photo [25,66]. Besides, the emerging multiple stimuli-responsive SMNs also open new avenues for exploration of DDSs, owing to their adaptation to complicated physiological environment to achieve excellent therapeutic efficacy [42].

Table 1
Examples of stimuli-responsive SMNs.

	Stimuli	Responsive moiety	References
Internal stimuli	pH	Acylhydrazone	[16,35,67,68]
		Ester	[15,48,59,69]
		Benzoic imine	[70]
		Carbamate	[3]
		Histidine	[51]
		Hydrogen bond	[4]
		Host-guest complex	[33,36]
	Redox	Disulfide	[31,43,58,71]
		Thioether	[64]
	Enzyme	Ester	[8,10,18,60,72]
External stimuli	Temperature	OEG dendrons	[73]
	Photo	Azobenzene	[25,66]
Multi-stimuli	Combination	Combination	[42,64,74]

3.2. Biocompatibility and biodegradability

Non-biocompatible or non-biodegradable external nanomaterials exhibit long-term accumulation in the human body, which is highly detrimental to the health of patients. Therefore, biocompatibility and biodegradability are of great importance for the exploitation of SMNs. From this perspective, SMNs have received increased attention in the biomedical field owing to their defined structure, excellent biocompatibility, controlled degradation process, and so on. In sharp contrast to conventional nanoscale DDSs, SMNs are self-assembled from small molecules, which can disassemble due to the dynamic nature of nano-assembly and then be degraded or metabolized after cancer therapy [18]. Moreover, SMNs possess defined structure and clear degradation product, which is beneficial for clinical translation. In addition, SMNs can be fabricated by self-organization of either natural molecules or versatile FDA-approved functional molecules as building blocks. For the former, various natural molecules have been used to construct SMNs, involving phospholipids [4,21], carbohydrates [16], peptides [79], amino acids [47], essential metal ions [22]. In addition, large numbers of FDA-approved functional molecules have also been widely used, such as targeting agents [80], imaging agents [18], vitamins [81] and drugs [15]. With the rapid development of chemistry and biology, more and more biodegradable and biocompatible SMNs will be designed for cancer therapy.

3.3. Unique metabolism pathway

Nanodrugs for cancer therapy have received great attention in recent years due to their prolonged blood residence time and preferential tumor accumulation [82]. However, most nanodrugs severely accumulate in the RES organs (such as liver and spleen), resulting in low tumor accumulation and poor treatment efficacy [83]. Moreover, the hepatic processing and biliary excretion are relatively slow, raising the risk of potential tissue damage and long-term toxicity [9]. On the contrast, small molecule anticancer drugs may undergo rapid renal excretion to completely excrete residual drugs after therapy to mitigate side effects [84]. Fortunately, as reported by Zhu and coworkers, SMNs could reveal the metabolism pathway of both nanoparticles and small molecules to achieve excellent tumor accumulation and then undergo rapid renal clearance after therapy [18] (Fig. 4). Zhu and coworkers designed nanoparticles self-assembled from amphiphilic small molecules, which was composed of CPT conjugated with magnetic resonance imaging (MRI) contrast agent Gd(DTPA) (DTPA, diethylene triamine pentaacetic acid). These Gd(DTPA-CPT) nanoparticles existed in rapid equilibrium shift with nanoparticles and small molecules during blood circulation and hence revealed the metabolism pathway of both nanoparticles and small molecules. *In vivo* MRI and biodistribution experiments demonstrated that these assembled nanoparticles could accumulate in tumors through passive targeting, while the dismantled ones were excreted via the kidneys in the form of free small molecules. Owing to the inherent equilibrium shift, small molecule nanoparticles integrated with obvious anticancer effect and low-toxic metabolism pathway for clinical applications.

4. Application of cancer therapy

As mentioned above, SMNs can display tailored properties and versatile functions with rational design, making them outstanding candidates for cancer therapy. Up to now, numerous SMNs have been explored and show great potential for therapeutic purposes [15,39]. In this section, we will summarize the recent advance of SMNs for cancer chemotherapy, including chemotherapy, combined therapy, and theranostics.

4.1. Chemotherapy

An ideal DDS should meet several criteria to satisfy the security requirements, such as exhibiting great anticancer efficacy and reduced side effects. Hence, these ideal DDSs should possess great biocompatibility along with biodegradability, achieve efficient tumor accumulation, and release parent drugs in tumor cells specifically. To date, SMNs have emerged as potentially ideal DDSs because of their facile fabrication and tailored property to meet those criteria. First of all, different from sophisticated synthesis of traditional DDSs, the synthesis route of SMNs is simple and

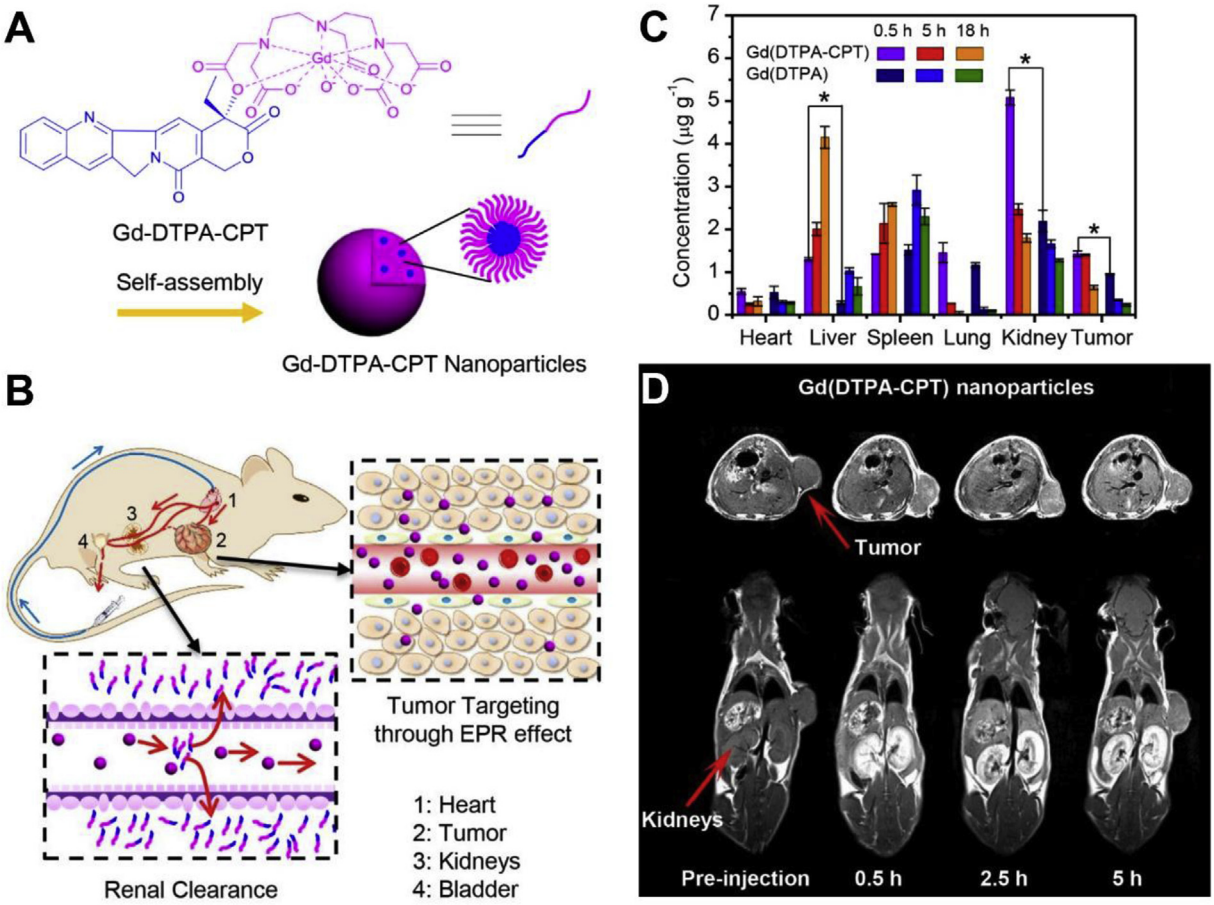

Fig. 4. Gd(DTPA-CPT) nanoparticles with tumor targeting and renal excretion property. (A) Schematic illustration of amphiphilic Gd(DTPA-CPT) self-assembly into nanoparticles. (B) Scheme of *in vivo* passive tumor targeting and renal clearance of Gd(DTPA-CPT) nanoparticles. (C) Biodistribution of Gd(DTPA-CPT) nanoparticles and Gd(DTPA) in various tissues bearing LoVo tumors. (D) *In vivo* T_1-weighted MR images of nude mice bearing LoVo tumors. Adapted with permission.[18] Copyright 2016, Ivyspring International Publisher.

reproducible, which can advance the manufacturing process and minimize batch-to-batch variation. Secondly, SMNs with appropriate size and shape can exhibit nano-characteristics such as prolonged blood circulation time as well as passive accumulation in tumor tissues via enhanced permeation and retention (EPR) effect [15]. Hence, most SMNs exhibit enhanced therapeutic efficacy and lower side effects than their parent drugs [18,39]. Moreover, to maximize the nano-characteristics *in vivo*, SMNs can possess tunable size and shape by adjusting their chemical composition and amphipathic property. Thirdly, in order to improve the drug delivery efficiency, tumor-targeting ligands can be introduced into SMNs. Finally, stimuli-responsive SMNs can selectively and rapidly release drugs after cancer cellular internalization. For the above mentioned reasons, various SMNs have expanded tremendously in recent years.

Up to now, tumor-targeting SMNs have emerged as potential DDSs to achieve high drug delivery efficiency and enhanced endocytosis [85]. Generally, the most commonly used targeting ligands for SMNs involve peptides [45,85], folic acid [80,86], lactose [16,71], and so on. These targeting agents can promote SMNs to recognize tumor cells, bind to specific receptors and hence facilitate cellular internalization via receptor-mediated endocytosis. For instance, Yan, Zhu and coworkers developed a novel tumor-targeting SMN consisting of targeting ligand lactose (Lac) and anticancer drug DOX [16] (Fig. 5). Hydrophilic Lac and hydrophobic DOX were conjugated via pH-responsive hydrazone group, and the amphiphilic Lac-DOX self-assembled into nanoparticles in aqueous solution. Thanks to the nano-characteristics, the *in vivo* assays indicated that Lac-DOX nanoparticles exhibited excellent tumor targeting ability, showed favorable pharmacokinetics, and possessed on-demand drug release behavior. Besides, due to the synergy of active and passive targeting ability, Lac-DOX nanoparticles mainly accumulated at the tumor site instead of major

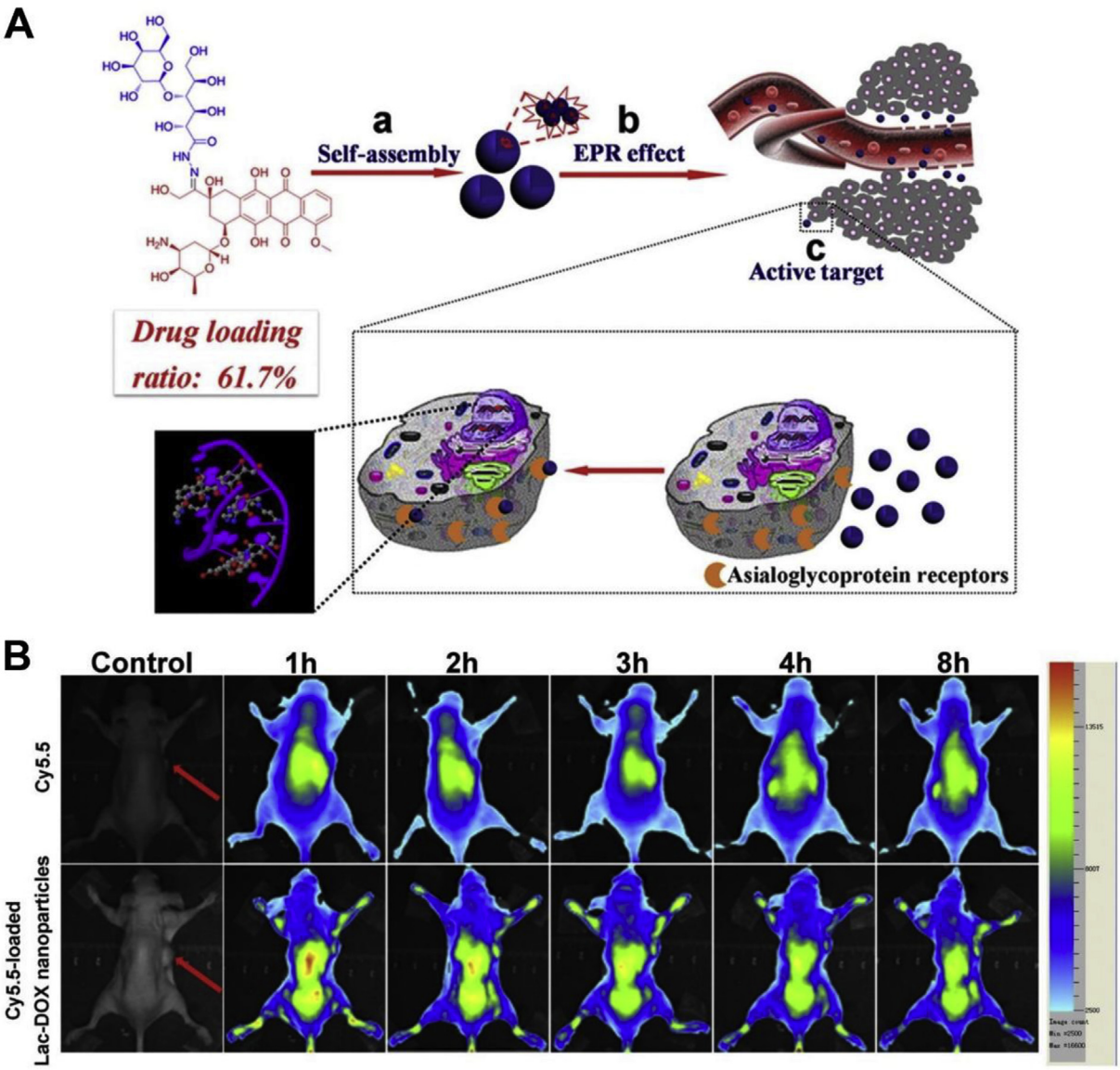

Fig. 5. Tumor-targeting SMN consisting of targeting ligand Lac and anticancer drug DOX. (A) Schematic illustration of Lac-DOX nanoparticles from fabrication, self-assembly to passive and active targeting drug delivery. (B) *In vivo* imaging of the tumor-bearing nude mice after intravenous injection of free Cy5.5 or Cy5.5-loaded Lac-DOX nanoparticles. Adapted with permission.[16] Copyright 2016, Elsevier.

organs, resulting in excellent therapeutic effect and weak side effects.

To date, numerous intelligent SMNs have gained great attention, owing to their negligible drug leakage during systemic circulation and rapid drug release in the pathological sites [68]. The stimuli-responsive properties of SMNs offer opportunities for the construction of intelligent nanodrugs. Till now, a great deal of stimuli-sensitive (including pH [51], redox [58], enzyme [62], thermal [73]) SMNs have been designed and investigated. For instance, Couvreur and coworkers reported conjugation of anticancer drug DOX onto biocompatible squalene (SQ) via esterase responsive ester linkage, which could self-assemble into "loop-train" nanostructure with 130 nm mean diameter [10] (Fig. 6). *In vitro* cell viability tests showed that SQ-DOX nano-assemblies (NAs) exhibited comparable antiproliferative and cytotoxic effects than their parent drug DOX owing to the effective drug release in tumor cells. Moreover, taking advantage of controlled release property and inherent nano-characteristics, SQ-DOX NAs displayed reduced side effects, negligible cardiotoxicity, and five-fold higher maximum tolerated dose (MTD) compared with DOX. In addition, the *in vivo* antitumor efficacy of SQ-DOX NAs was investigated on human pancreatic and murine lung carcinomas, which were very difficult to cure and resistant to native DOX. Thanks to their low side effects and high MTD, SQ-DOX NAs could show excellent anticancer efficacy, such as

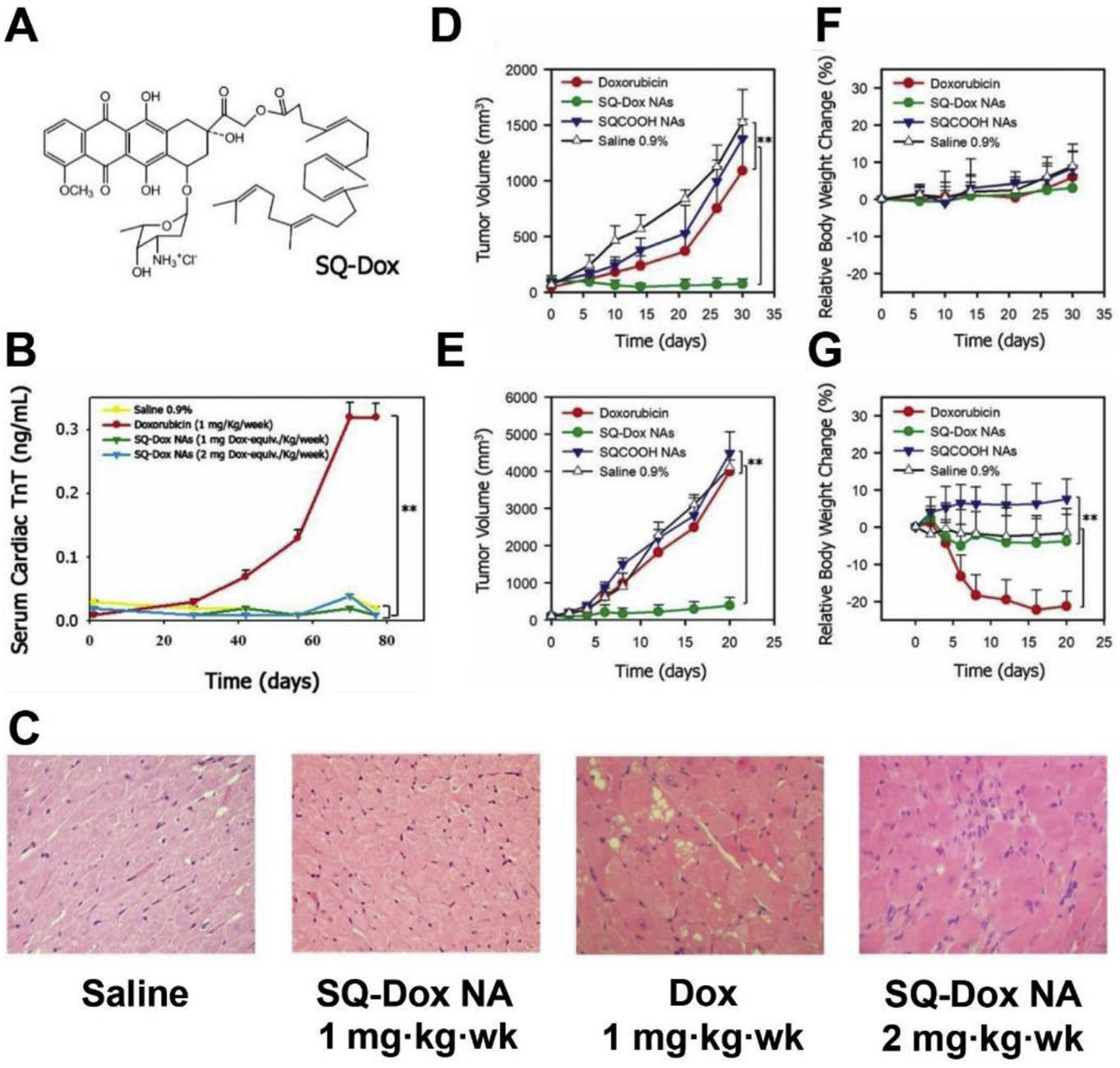

Fig. 6. SQ-DOX NAs display reduced cardiotoxicity and excellent antitumor efficacy. (A) Chemical structure of SQ-Dox NAs. (B,C) Evaluation of the cardiotoxicity induced by DOX. (B) Time course of serum concentrations of cardiac troponin-T (TnT) in hypertensive rats. (C) Hematoxylin-Eosin-Safran (HES) stained sections of cardiac tissue (left ventricular inner myocardium) of SH male rats. (D–G) Anti-tumor activity of SQ-Dox NAs and the body-weight changes of mice bearing MiaPaCa-2 tumors (D and F) or M109 tumors (E and G). Adapted with permission.[10] Copyright 2014, PNAS.

95% inhibition of MiaPaCa-2 pancreatic tumors and 90% inhibition of M109 lung tumors, which was far higher than the treatment effect of free DOX.

4.2. Combined therapy

Pure chemotherapy remains unsatisfactory for completely curing cancer, for it always suffers from insufficient therapeutic efficacy, serious drug resistance and dose limiting toxicity [87]. These deficiencies have inspired combined therapy which produces additive, synergistic, and complementary interactions between different treatments. SMNs can also integrate with other therapeutic agents to achieve multifunctional therapeutic platforms for combined therapy. Up till now, various therapeutic methods have been involved in the platform of SMNs, such as gene therapy and photodynamic therapy (PDT) [22,43,88].

Gene therapy represents a promising approach for cancer treatment by transferring genetic genes into the disease site [89]. These genetic materials can adjust gene expression, regulate the amount of proteins, or generate cytotoxic proteins, all of which play important roles in the survival and progression of cancer cells [90]. Hence, it is of great significance to develop co-delivery system for drug and gene to achieve synergistic effect. For instance, to circumvent MDR, Cheng and coworkers designed a SMN to co-delivery CPT and small interfering RNA for MDR cancer therapy [43] (Fig. 7). They synthesized a drug-peptide conjugate CPTssR5H5 via disulfide linkage, which self-assembled into liposome-like vesicles to condense siRNA. The obtained CPTssR5H5-siRNA complex could achieve high therapeutic effect and high transfection efficiency. *In vitro* experiments indicated that CPTssR5H5-siRNA complex was a promising co-delivery system for MDR cancer therapy.

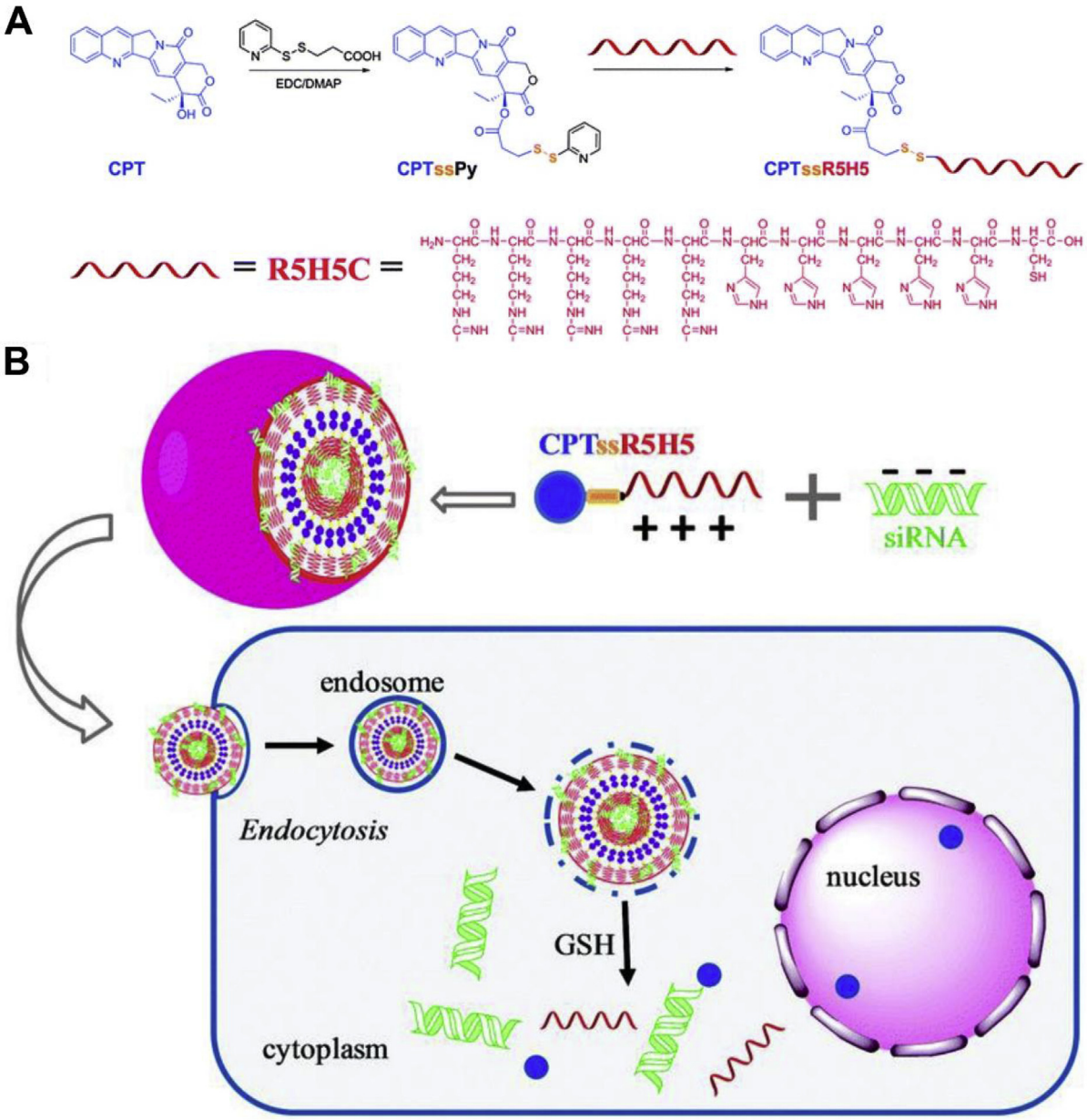

Fig. 7. Co-delivery system of CPTssR5H5-siRNA complex for MDR cancer therapy. (A) Synthetic route of CPTssR5H5. (B) Illustration of a co-delivery system CPTssR5H5 to deliver CPT and MAP3K7-targeted siRNA simultaneously to MDR cancer cells for enhanced chemotherapy. Adapted with permission.[43] Copyright 2014, Royal Society of Chemistry.

PDT is another promising therapeutic modality for cancer treatment owing to its noninvasiveness and high selectivity [91]. PDT utilizes nontoxic photosensitizer (PS) to transfer photo-energy to surrounding intracellular oxygen to generate ROS, which can induce cell death and necrosis of proximal tissues [92]. Hence, PDT can be used along with chemotherapy to provide synergistic effects for cancer treatment. For example, Lee and coworkers designed a self-delivered PS-doped SMN, which was composed of perylene and 5,10,15,20- tetro (4-pyridyl) porphyrin (H_2TPyP) co-doped into anticancer drug curcumin (Cur) matrix [88] (Fig. 8). Perylene and H_2TPyP co-doped NPs exhibited specific fluorescent properties and hence endowed the system with imaging and real-time self-monitoring capabilities. *In vitro* cell viability demonstrated that this "PDT + chemotherapy" nanodrug resulted in much higher toxicity than either chemotherapy or PDT alone. Besides, owing to the combined therapy, the co-doped NPs exhibited significant tumor inhibition *in vivo* and showed high biosafety without significant side effects to the mice.

4.3. Theranostics

Theranostic platforms based on various modes of imaging have been successfully developed and extensively applied in the field of nanodrug, which can help to track delivery behavior, monitor drug release process, and evaluate therapeutic efficacy [93]. Till now, different kinds of imaging techniques, such as optical imaging [94], MRI [18] and so on have been integrated with SMNs to develop theranostic platforms.

Optical imaging is a powerful imaging modality due to its high sensitivity and spatial resolution as well as its switchable signal [76]. Hence, various kinds of fluorescent probes have been used for theranostic SMNs, such as organic fluorescent dyes and some

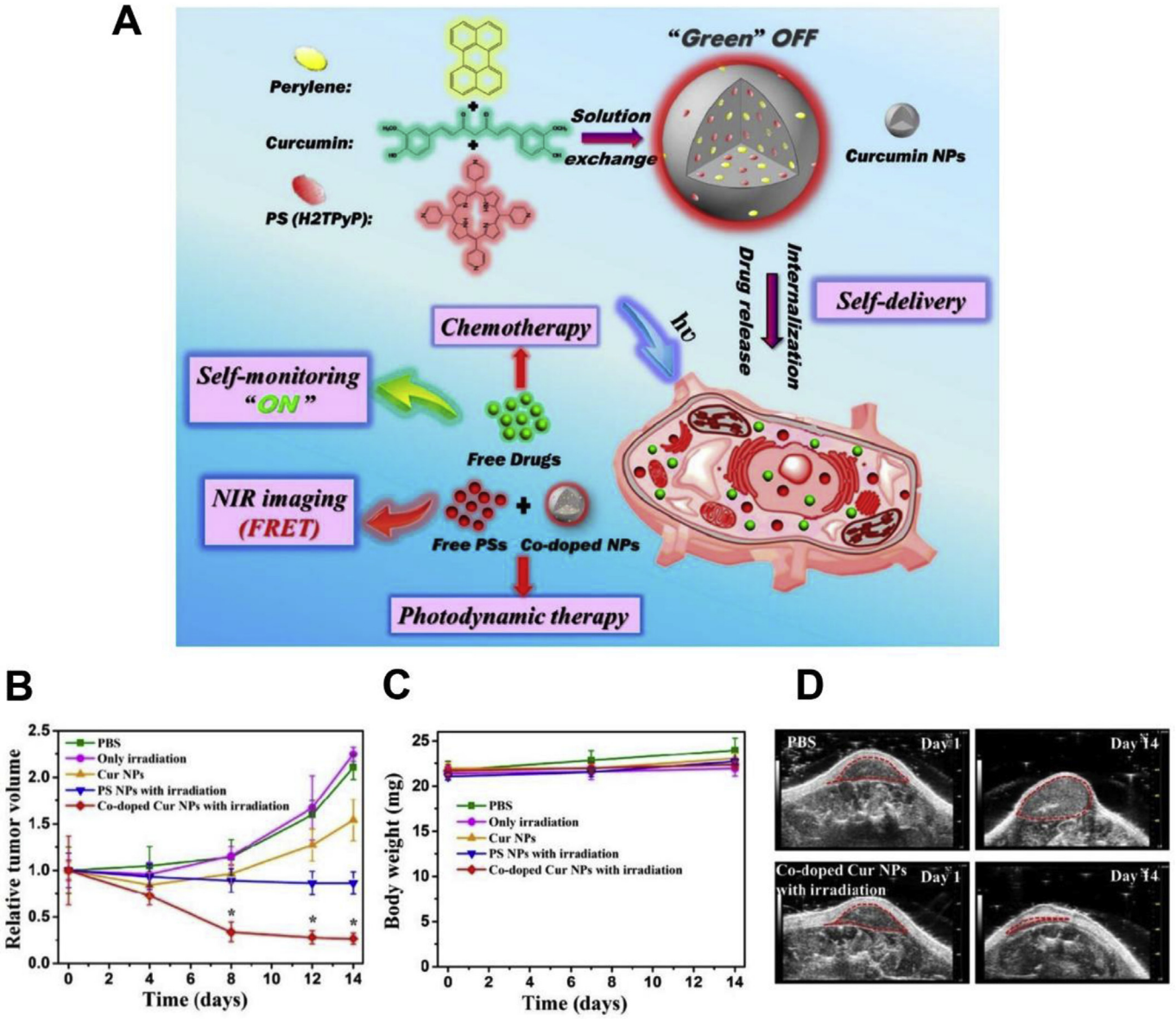

Fig. 8. Perylene and H_2TPyP co-doped Cur matrix for chemophotodynamic therapy. (A) Schematic illustration on the synthesis of the H_2TPyP and perylene co-doped Cur NP and its application for self-delivered and self-monitored chemophotodynamic theranostics. (B) *In vivo* antitumor activity of the co-doped NPs on A549 subcutaneous xenograft model. (C) Body weights of mice after treatment. (D) Ultrasound images of A549 lung tumor xenograft before and after treatment with PBS and the co-doped NPs with irradiation, respectively. Adapted with permission.[88] Copyright 2015, American Chemical Society.

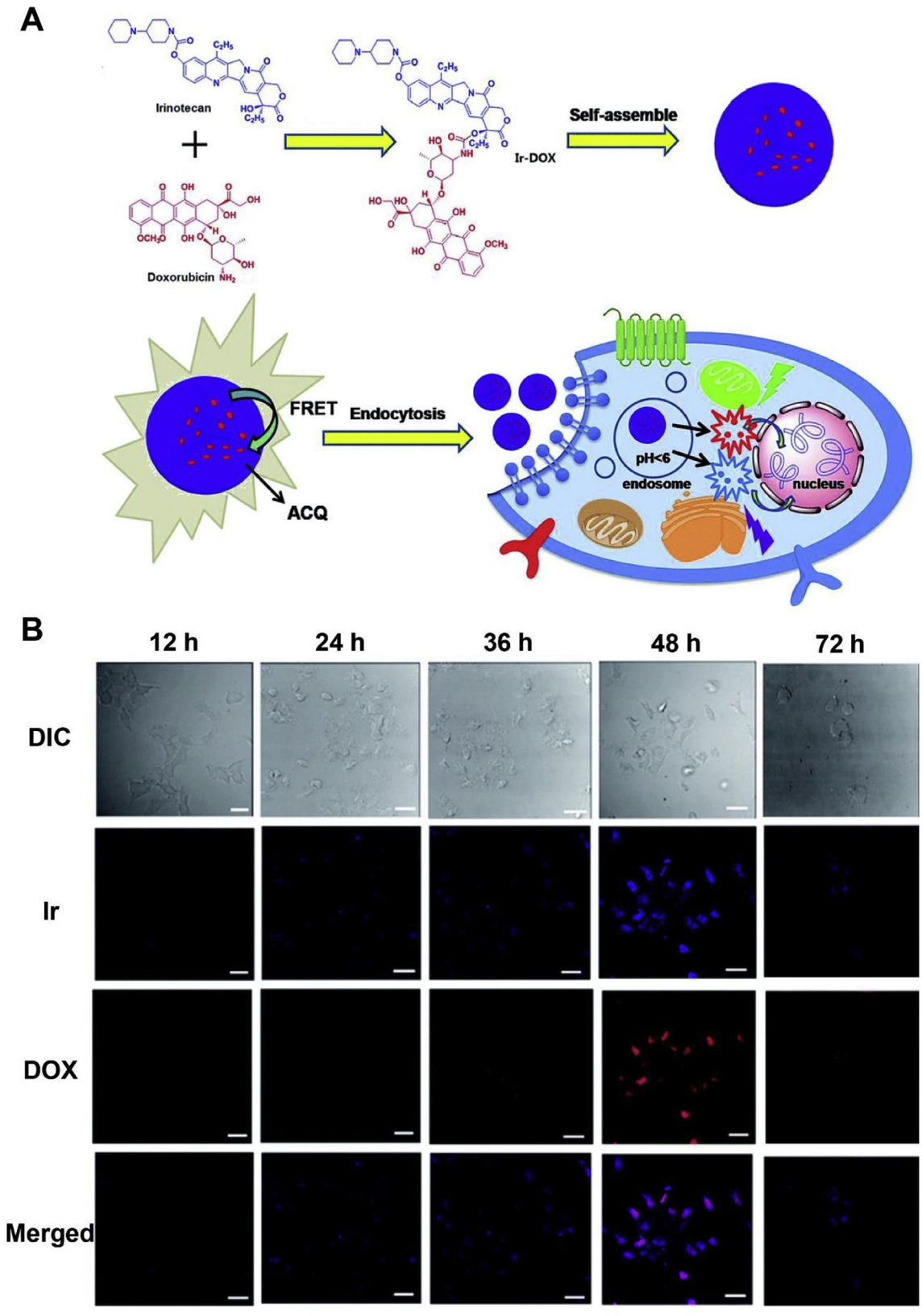

Fig. 9. Real-time self-tracking Ir-DOX SMN based on colorful fluorescence variations. (A) Ir-DOX conjugate and the construction of the self-assembled micelles for self-tracking cancer therapy. (B) Fluorescence images of MCF-7 cells treated with Ir-DOX micelles at different time intervals. Adapted with permission.[3] Copyright 2016, Royal Society of Chemistry.

anticancer drugs with fluorescent property. These theranostic nanodrugs can achieve real-time tracking of the drug delivery and release process [25,95]. For instance, Zhu and coworkers prepared a self-tracking SMN, which was constructed by conjugation and self-assembly of hydrophobic DOX and hydrophilic Ir via carbamate linkage [3] (Fig. 9). Due to great overlap between the emission of Ir (donor) and the excitation of DOX (acceptor), an efficient fluorescence resonance energy transfer (FRET) was observed for Ir-DOX conjugate in their good solution. Owing to its inherent amphiphilicity, Ir-DOX conjugate could self-assemble into micelles in water and subsequently quench the fluorescence for aggregation-caused quenching (ACQ). This assembly-related fluorescent property was used for tracking of drug delivery and release process of Ir-DOX nanodrug. *In vitro* cell imaging experiments revealed that no obvious fluorescence was observed during 12 h cell incubation with Ir-DOX. This indicated that Ir-DOX entered cells in the form of nanoparticles instead of free conjugate or free drugs. With increasing incubation time, the Ir-DOX linkage was broken to release free drugs, leading to the recovery of dual-color fluorescence. This Ir-DOX SMN provided an opportunity for real-time self-tracking of probe-free and carrier-free drug delivery systems for cancer treatment.

MRI is one of the most powerful imaging techniques for theranostics due to its high spatial resolution, deep tissue penetration and noninvasiveness [96]. In order to enhance the sensitivity of MRI, various contrast agents (CAs) have been widely explored, such as T_1-weighted CAs (gadolinium complex, manganese complex, etc.) or T_2-weighted CAs (iron oxide particles, etc.) [97]. The integration of MRI CAs with SMN can be utilized to monitor the drug delivery process *in vivo* to investigate the biodistribution and metabolism pathway of SMNs. For instance, Zhu and coworkers constructed amphiphilic small molecules consisting of CPT conjugated with MRI CAs Gd(DTPA) [18]. The obtained Gd(DTPA-CPT) could self-assemble into nanoparticles in water, holding the capabilities of imaging and chemotherapy. *In vivo* MRI experiments demonstrated that Gd(DTPA-CPT) nanoparticles could accumulate in tumor tissues owing to the EPR effect, while the small molecules dismantled from the nanoparticles could be efficiently cleared by kidneys. Therefore, the renal-clearable nanoparticles exhibited excellent antitumor efficacy and negligible side effects. These results demonstrated a potential strategy for SMN with obvious anticancer effect and low-toxic metabolism pathway for clinical applications.

5. Conclusions and perspective

In this Review, we summarized the tremendous progress in the exploitation of SMNs, including their design and synthesis, biological properties and wide applications in the field of cancer therapy. The rapid growth of SMNs is mainly attributed to the facile fabrication and unique biological properties. Firstly, compared with traditional nanoscale DDSs, SMNs possess defined structure with simple synthesis route, which is appealing for industrial production and clinical translation. Secondly, SMNs achieve extremely high drug loading ratio and release the burden of carriers to the body during therapy. Thirdly, SMNs can combine both advantages of nanoscale DDSs and small molecules, including enhanced blood circulation, excellent tumor accumulation, and low-toxic metabolism pathway. Therefore, SMNs have become excellent candidates for cancer therapy. These unique advantages contribute to the versatile applications of SMNs for cancer therapy.

Despite achieving enormous progress, this area still faces several key challenges. Firstly, compared with versatile traditional nanoscale DDSs, the design of SMNs is a big challenge due to the limitation in adjusting the hydrophilic-hydrophilic balance of each component. Hence, in comparison with traditional nanoscale DDSs, SMNs exhibit less tenability in the resulting drug loading ratios and morphologies, which have great impact on the biodistribution, cellular interaction and therapeutic efficacy. In addition, different from traditional nanoscale DDSs, SMNs is composed of small molecule units, which may possess smaller size and higher penetrability in the tissues. Considering these superiority of small molecule units, optimal SMNs should be explored to overcome multilayered stromal cell barrier for deeper tumor penetration and increased drug perfusion. Moreover, in order to understand the drug delivery process and metabolic pathway in the body, it is of great importance to achieve real-time tracking of SMNs during systemic circulation and clarify their biodistribution. What's more, to further understand the drug action mechanism, it is important to study the interaction between tumor cell and SMNs such as cellular internalization, transportation, excretion.

As a final remark, it is a long way to convert SMNs into marketable products for biomedical application. But we firmly believe that the rapid development of this field will resolve the problems from large-scale production to clinical application in the future.

Acknowledgments

The authors thank the National Basic Research Program (2015CB931801) and the National Natural Science Foundation of China (51690151, 51473093).

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