Chemical Engineering Journal 495 (2024) 153438

Contents lists available at ScienceDirect

Chemical Engineering Journal

journal homepage: www.elsevier.com/locate/cej

Review

Micelle-engineered nanoplatforms for precision oncology

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ARTICLE INFO

Keywords:
Micelles
Cancer therapy
Cancer diagnosis
Drug resistance
Gene therapy

ABSTRACT

The alliance between nanomaterials and cancer therapy has revolutionized the treatment of tumor patients. After cardiovascular diseases, cancer is the leading cause of death, so interdisciplinary approaches should be used for the treatment of this malignant disease. Both treatment and early diagnosis of cancer are challenging. The micelles belong to lipid-based nanostructures, and they have a hydrophobic core with hydrophilic head regions. The current review article focuses on the application of micelles in cancer suppression. The micelles can provide a platform for co-delivery of non-coding RNAs and RNAi in cancer gene therapy. Both synthetic and natural

Abbreviations: MRI, magnetic resonance imaging; CT, computed topography; TME, tumor microenvironment; RNAi, RNA interference; siRNA, small interfering RNA; shRNA, short hairpin RNA; LA, linoleic acid; ncRNAs, non-coding RNAs; RISC, RNA-induced silencing complex; miRNAs, microRNAs; PTX, paclitaxel; DTX, docetaxel; DOX, doxorubicin; CP, cisplatin; BBB, blood-brain barrier; FA, folic acid; TPZ, tirapazamine; TPZD, TPZ detivatives; CSCs, cancer stem cells; NSC, niclosamide; TAMs, tumor-associated macrophages; ROS, reactive oxygen species; EPR, enhanced permission and retention; GSH, glutathione; UV, ultraviolet; NIR, near infrared; PTT, photothermal therapy; PDT, photodynamic therapy; HA, hyaluronic acid; Tf, transferrin; HSDs, heparosan and deoxycholic acid conjugates; DTPA, diethylenteriominepent acetic acid; PEG, poly(ethylene glycol); CAC, critical aggregation concentration; CMC, critical micelle concentration; PICM, polyion complex micelles; DMSO, dimethylsulfoxide; DMF, dimethylsulfoxid e; DMF, N,N-dimethylfermamide; ACN, acetonitride; THF, tetrahydrofuran; PEG, poly (ethylene gycol); VP, vinyl pyrrolidone; FAS, ferrous ammonium sulphate; APS, ammonium persulphate; PCL, PEG-block-poly(ε-caprolactone); TRPV1, transient receptor potential cation channel subfamily V member 1; ICG, indocyanine green.

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https://doi.org/10.1016/j.cej.2024.153438
Received 3 April 2024; Received in revised form 6 June 2024; Accepted 22 June 2024
Available online 24 June 2024

compounds with anti-tumor activity can be delivered by micelles. Besides, the co-delivery of drugs and genes mediates synergistic cancer therapy. Various kinds of smart micelles, including pH-, light-, redox- and multi-sensitive micellar nanostructures, can support targeted cancer treatment. The modification of micelles with ligands such as hyaluronic acid and aptamers can enhance the selectivity of nanostructures toward tumor cells. The micelles can also be employed for cancer diagnosis. The combination of micelles with other nanostructures, such as polymeric nanoparticles, is served to improve cancer treatment. The studies demonstrate the high biocompatibility and safety profile of micelles. The green modification and synthesis of micelles can enhance their biocompatibility. Therefore, micelles can be utilized in the near future for the treatment and diagnosis of cancer patients.

1. Introduction

After cardiovascular diseases, cancer is one of the leading causes of death worldwide. The treatment of cancer depends on combining various fields, including engineering and biology. Therefore, recent studies have focused on the introduction of nanomedicine in cancer therapy [1,2]. Efforts have been made in the diagnosis and treatment of cancer. Imaging and morphological analysis of tissues are considered as some of the techniques for cancer diagnosis at early stages [3]. Magnetic resonance imaging (MRI), computed tomography (CT), endoscopy, and ultrasound are among the diagnostic tools for cancer [3]. Regardless of diagnosis, treatment, and management of cancer are challenging, and there have been efforts to develop novel therapeutic modalities for cancer. Nanotechnology is a new emerging field for cancer treatment that aims at developing and fabricating nanostructures with sizes of 1–100 nm, and they have at least one dimension. The size and composition of nanostructures can be tuned making them an appropriate choice in the field of medicine and biology [4]. The nanostructures can help in the diagnosis and treatment of various diseases, especially cancer, and they are widely utilized for cargo delivery. The cargo can be gene, drug, or both, and the nanostructures are capable of encapsulating cargo, promoting their blood circulation time, and improving their therapeutic index. The nanotechnological approaches can also be beneficial in bioimaging and cancer immunotherapy, which have been in demand in recent years. Furthermore, green chemistry can contribute to improving the biocompatibility of nanocarriers and paving the way for clinical translation [5].

Regarding the high mortality and morbidity resulting from cancer and the inability of conventional treatments for this threatening disease, the development of nanoparticle-based strategies can significantly help in the cancer fight. In recent years (2023), there have been a number of reviews about the application of micelles in cancer therapy. However, their approach to investigation is limited, as they have focused on only a few aspects of cancer therapy, such as using micelles in cancer immunotherapy [6], development of tumor microenvironment-responsive micelles [7], and using dendrimer micelles in cancer drug delivery [8]. However, different aspects of using micelles in cancer gene delivery, bioimaging, their functionalization, hybrid nanoparticles, theranostic application, and stimuli-responsive micellar nanoparticles have been ignored. Therefore, the current comprehensive review article evaluates these subjects to provide a detailed description of using micelles in cancer therapy for various purposes, from drug and gene delivery, chemotherapy, and immunotherapy to functionalization, theranostics, stimuli-responsive structures, and bioimaging.

The current review aims to evaluate the potential of micelles in the treatment of cancer. At first, the structures of micelles and common strategies for their fabrication and synthesis are described. Then, the role of micelles in drug and gene delivery is highlighted, and their ability to provide a platform for the co-delivery of genes and drugs in synergistic cancer therapy is shown. Then, we focus on developing smart micellar nanoparticles that are responsive and can provide tumor site release of cargo. Then, the role of micelles in imaging, their internalization in cancer cells, surface modification, and biosafety profile that is of importance for clinical application are discussed.

2. Structure and fabrication

Amphiphilic molecules have well-defined domains of hydrophobic/hydrophilic features. Micelles are formed by the dynamic aggregation of these amphiphilic molecules due to the hydrophobic effect in aqueous solution and the formation of hydrogen bonds [9,10]. In a normal micelle, the nonpolar segment of the molecule is known as a hydrophobic tail, while the polar (hydrophilic) segment is named the head group [11]. The normal micelle can be dissolved in an aqueous medium. As the concentration of these molecules increases above a certain value (called the critical aggregation concentration (CAC) or the critical micelle concentration (CMC)), the surfactant molecules aggregate to form micelle aggregations [12–14]. On the other hand, hydrophobic sections of block copolymers (at the CAC or CMC) are so close together that they have minimal contact with water molecules and eventually form a vesicular or core–shell micellar structure [15]. One of the important surface properties of surfactants is CMC because it can affect other features such as conductivity, density, viscosity, surfactant activity coefficient, and osmotic coefficient. If the concentration is less or more than CMC, the thermodynamic properties alter significantly [16–18].

Different types of micelles consist of regular, reverse, and unimolecular micelles (Fig. 1) [19], which generally are divided into two categories, including surfactant micelles (with low molecular weight) and polymeric micelles. Polymeric micelles are known as molecules with a nucleus-shell structure in the nanoscale. In the presence of an aqueous solvent, these materials are able to form their own micelle-shell structure through the self-assembling of amphiphilic block copolymers [20]. The core–shell structure of polymeric micelles affects their performance so that the hydrophobic core is able to carry the drugs or protect their loaded dosage. Simultaneously, the hydrophilic shell plays the role of supporting, stabilizing and creating a suitable solubility of the hydrophobic nucleus in aqueous media.

A variety of methodologies have been proposed for the micelles preparation, including (i) simple dissolution, (ii) dialysis, (iii) oil in water emulsion, (iv) solvent evaporation, and (v) lyophilization or freeze-drying [21]. The direct dissolution method usually uses copolymers with relatively high solubility in water with or without the drug in aqueous medium (such as deionized distilled water or buffer). In this method, depending on the need, other conditions such as stirring, heating and/or ultrasound may be added to load the drug into the nanomicelles. Core dehydration eventually leads to micelle formation [21]. For instance, poloxamers are used in this method to prepare polyion complex micelles (PICM). After the separate dissolution of copolymers and drugs in aqueous media, micelles are formed with a suitable combination of proportions of them [22,23].

If the solubility of amphiphilic copolymer in water is low, the dialysis technique is often used to prepare micelles. In this method, various organic solvents (such as dimethylsulfoxide (DMSO), *N,N*-dimethylformamide (DMF), acetonitrile (ACN), tetrahydrofuran (THF), acetone, and dimethylacetamide) are applied for dissolving polymers and drugs with a suitable ratio. By adding this copolymer-solvent mixture to the water-aqueous solvent, micelles are formed. After micelle formation, a dialysis technique was utilized to remove water media from the system. It is worth noting that the choice of solvent type

affects the micelle properties (viz., their micelle size, stability, and loading capacity of the drug). It should not be forgotten that if the organic solvent used in water was miscible, the dialysis time to remove the organic solvent should be longer [21,24–26]. If the copolymer and the drug are both dissolved in an organic solvent, some cosolvents (such as dimethylacetamide and *tert*-butanol) with high vapor pressure are exerted to fast sublimate the solvent and lyophilization (freeze-drying), respectively. Micelles prepared by this technique not only possess high dispersibility in water but also illustrate high durability/ shelf-life [27–29].

This micelle type can be prepared via the oil-in-water microemulsion methodology [30]. Accordingly, these micelles can be used to encapsulate and increase the solubility of insoluble drugs. Polymeric micelles are usually composed of three different types of polymers, including diblock −block copolymers (such as polystyrene and poly (ethylene glycol) (PEG)), three-block copolymers (such as poly (ethylene oxide)) and graft copolymers (such as stearic acid and G-chitosan) [20]. In contrast, other groups of micelles (called reverse micelles) have a hydrophilic nucleus and a hydrophobic crust that form through water-in-oil. Some drugs (such as doxorubicin as anti-tumor antibiotics) can chemically interact with OH functional groups of poly lactic-co-glycolic acid of a diblock copolymer micelles or entrap into the same micelle via physical interaction [31].

Lock copolymer micelles are classified according to the kinds of intermolecular forces. In fact, these intermolecular forces separate the nucleus segment from the aqueous medium. The longer the hydrophilic part forms the spherical micelle, but as the length of the nucleus extends beyond the corona-forming chains, it creates non-spherical structures such as rods and lamellae. Accordingly, lock copolymer micelles are divided into three main categories- amphiphilic micelles, PICM, and micelles due to metal complexes [32]. For instance, a copolymer of N-isopropyl acrylamide (NIPAAM) NIPAAM/ vinyl pyrrolidone (VP)/ acrylic acid (AA) can be synthesized through the free radical mechanism. These monomers with a molar ratio of 85.7:9.5:4.8 were applied along with N, N%-methylene bis-acrylamide (MBA) as a cross-linker. Ferrous ammonium sulphate (FAS) and/or ammonium persulphate

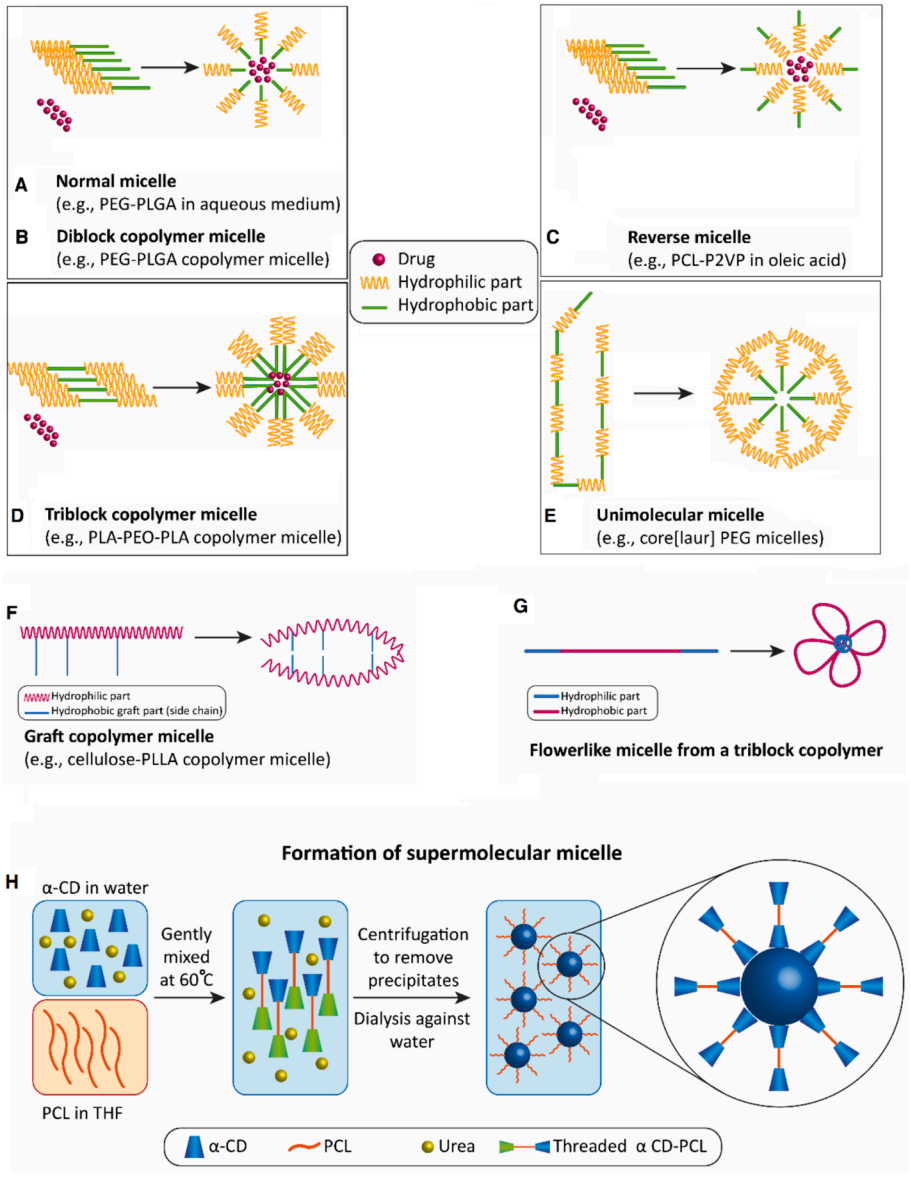

Fig. 1. Different kinds of micelles [19]. The normal (A), reverse (B), and unimolecular micelles (C) are prepared from aqueous medium, organic medium, and amphipathic molecules. In normal micelles, the hydrophilic regions are located on the outside, while hydrophobic regions are located on the inside. In the reverse micelles, hydrophobic regions are located on the outside, while hydrophilic regions are located on the inside. Furthermore, A-G parts demonstrate that micelles can be fabricated from polymers. Part H demonstrates the formation of supramolecular micelles.

(APS) are usually used as initiators in the preparation process to activate the reaction of polymerization and achieve a good yield (>80 %). The polymerization process can be performed in a nitrogen atmosphere. This copolymer can also be lyophilized to obtain a dry powder product [33]. In other research, a block copolymer including PEG-*block*-poly(ε-caprolactone) (PCL) (PEG-*b*-PCL) was selected as biodegradable, amphiphilic, and photothermal polymeric micelles. The indocyanine green entrapped into the micelles forgives excellent photothermal effects and NIR emission to activate neurons via transient receptor potential cation channel subfamily V member 1 (TRPV1). Polymeric micelles containing indocyanine green (ICG-micelles) loaded with anti-TRPV1 antibodies effectively bound TRPV1 on cell membranes, and accelerated Ca^{2+} ion influx into neuronal cells was induced under NIR irradiation. Based on these findings, it is anticipated that the ICG micelles can serve as a novel noninvasive remote-activation tool for neuronal cells [34].

3. Drug delivery: Emphasis on chemotherapy drugs and natural products

The cancer cells demonstrate unique and abnormal features compared to normal cells and the most well-known ones are high proliferation rate, cell cycle progression, and ability to migrate into neighboring and distant cells and tissues. These abnormal characteristics of tumor cells have been under attention in the field of cancer therapy. In fact, different kinds of anti-cancer agents, including both synthetic and natural products, have been developed to minimize the progression of tumor cells and improve the prognosis of cancer patients. The most well-known chemotherapeutic agents include paclitaxel (PTX), docetaxel (DTX), doxorubicin (DOX), and cisplatin (CP), among others, are widely employed for the purpose of tumor suppression. The reason for the development of various anti-cancer agents is the capacity of tumor cells to achieve resistance. However, there is still a high chance of drug resistance development in cancer patients, and this is one of the reasons responsible for chemotherapy failure and death of cancer patients around the world [35]. According to the presence of drug resistance, new kinds of anti-cancer compounds derived from nature were utilized in the field of cancer therapy. The naturally occurring compounds have a variety of benefits, including multi-targeting capacity and low adverse effects. Furthermore, the resistance of cancer cells to plant-derived natural compounds has not been reported yet. Therefore, they are promising agents in the field of cancer therapy [36,37]. Noteworthy, combination cancer therapy using natural and synthetic compounds with anti-tumor activity is followed to eradicate this malignant condition, and it has been successful. However, complete treatment of cancer requires developing nanoplatforms for the delivery of these anti-tumor agents. In fact, the internalization of anti-cancer agents, their long blood circulation, and penetration via impediments such as the blood–brain barrier (BBB) should be improved, and nanostructures are of interest in this case. The present section focuses on the application of micellar nanostructures for the delivery of anti-cancer agents.

3.1. Delivery of chemotherapy drugs

The micelles have shown high potential for delivery of chemotherapeutic drugs with the purpose of tumor suppression. DOX shows cytotoxicity against various tumors, including lung and ovarian cancers. However, its efficacy should be improved in complete eradication of cancer cells. A recent experiment has developed micellar nanoparticles for DOX delivery in the treatment of ovarian and lung cancers. The micelles were prepared from a deblock copolymer mPEG-*b*-PLA and a graft polymer (P(HPMA-Lac-*co*-His)-g-PLA), and ring-opening polymerization was used for their preparation. The resulting micelles had a particle size of 200 nm with high stability, so they preserved their homogenous particles after 72 h incubation in physiological conditions. The micelles undergo swelling in an acid environment (similar to TME) and release their cargo. This promotes cytotoxicity of DOX by its release at the tumor site. The DOX-loaded micelles effectively penetrated cancer cells and were found in *endo*-lysosomes. After 24 h, DOX was localized in the nucleus of cancer cells to exert its anti-tumor activity. The biodistribution study demonstrated the localization of DOX-loaded micelles

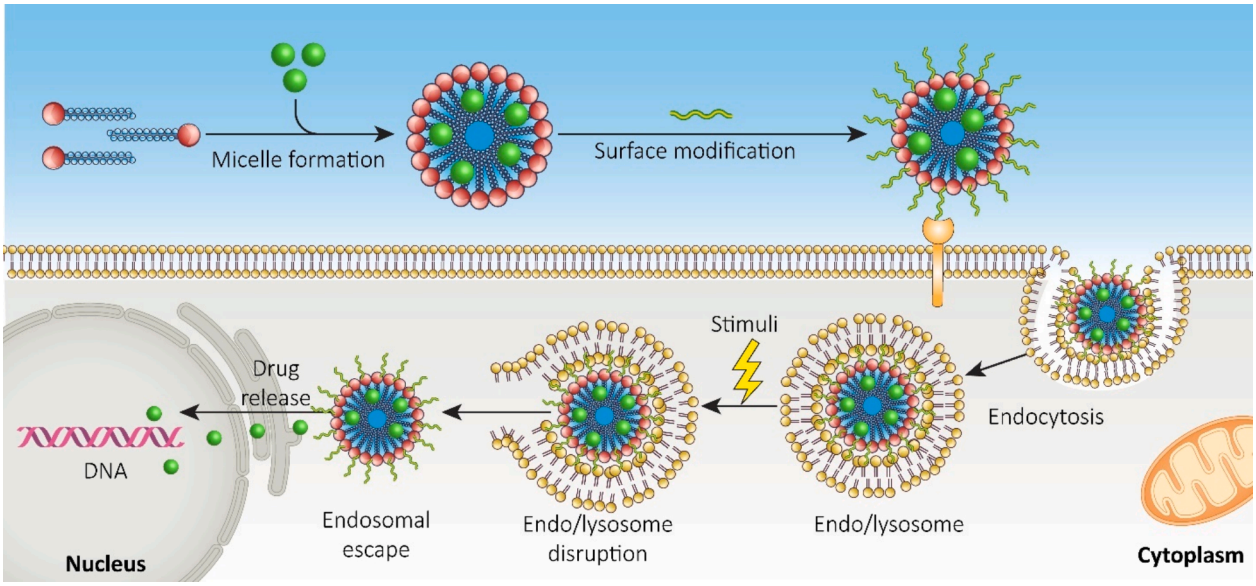

Fig. 2. A schematic representation of the endocytic pathway followed by micelles for internalization in tumor cells and subsequent release of cargo upon endosomal escape. The most common strategy utilized by he nanoparticles for the internalization in tumor cells is through endocytosis. The endocytosis depends on various factors such as shape, size, and surface charge of nanoparticles. One of the most well-known strategies for mediating endocytosis is the modification of nanoparticles with ligands to provide their receptor-mediated endocytosis. The identification of receptors overexpressed on the surface of tumor cells and then, modification of micelles with the corresponding ligands can mediate endocytosis. Evaluation of endocytosis is of importance, since rigid nanoparticles demonstrate low internalization in tumor cells, while micellar display favorable internalization and subsequent modification with ligands for improving endocytosis and internalization can improve the potential of these structures in the delivery. Regarding the small size of micelles and their ability for the endocytosis, the micellar nanoparticles are promising candidates for the delivery approaches in cancer therapy.

in different organs, but their localization was higher in tumor tissues compared to spleen and liver (1.5- and 2-fold more accumulation at tumor site compared to spleen and liver). The in vivo experiment on mice revealed reduced tumor volume upon application of DOX-loaded micelles, and these nanostructures induced apoptosis to reduce cancer growth. The release of DOX from these micelles was pH-responsive to mimic the conditions of the tumor microenvironment (Fig. 7) [38]. In addition to ovarian and lung cancer cells, micelles have been employed for DOX delivery in the treatment of breast and cervical cancer cells. A recent experiment developed PCL-*b*-PMPC micelles using atom transfer radical polymerization for DOX delivery, and its modification with folic acid (FA) was performed. The reason for using PCL-*b*-PMPC in the synthesis of micelles is their biocompatibility, safety profile, and biodegradability. The zwitterionic polymeric micelles comprised of aldehyde functional groups were prepared using self-assembly occurring between poly(2-methacryloyloxyethyl phosphorylcholine-b-poly(di(ethylene glycol) methyl ether methacrylate-co-4-formylphenyl methacrylate) [PMPC-b-P(DEGMA-co-FPMA)]. Then, the polymer-drug conjugate was obtained by grafting tirapazamine (TPZD) into PMPC-b-P(DEGMA-co-FPMA), which contained an imine bond responding to pH. Then, DOX, as an anti-cancer agent, was loaded on nanocarriers. The prepared micelles demonstrated a particle size of 158 nm, and upon exposure to mildly acidic pH 5.0, the release of DOX occurs for effective cancer suppression. These micelles significantly enhanced the internalization of DOX in tumor cells (MCF-7 and HeLa cells), and MTT assay revealed their high biocompatibility and low toxicity towards normal cells (L929 cells) [39].

The interest in using nanostructures for the delivery of anti-cancer agents emanates from the low efficacy of chemotherapeutic agents in clinical courses. Although cisplatin is widely applied in clinical trials, the efficacy of this drug can be improved using micellar nanoparticles. The polymeric micelles have been prepared from sodium poly(α-l-glutamic acid)-graft-methoxy-polyethylene glycol (PLG-G-PEG5K) to encapsulate cisplatin and vinorelbine. Then, these drug-loaded micelles were embedded into liposomes through a reverse evaporation strategy to develop co-drug-loaded liposomes containing egg phosphatidyl lipid-80/cholesterol/DPPG/DSPE-mPEG2000 at a molar ratio of 52:32:14:2. In addition to the uniform size distribution, the nanocarriers had 162.97 nm particle size along with zeta potential of −13.02 mV. These nanocarriers exerted a synergistic impact in the treatment of lung cancer along with improving the half-life of drugs. Due to the EPR effect, they increased the accumulation of drugs at the tumor site [40]. These studies highlighted the fact that cancer cell suppression can be boosted using micelles for cancer drug delivery. One of the new highlights in tumor treatment is affecting cancer stem cells (CSCs). Overall, CSCs possess self-renewal capacity, and they can differentiate into cancer cells. The CSCs are responsible for an enhanced population of tumor cells and also cancer recurrence. Therefore, anti-cancer agents targeting CSCs have been developed. Niclosamide (NSC) is an anti-tumor agent developed to target CSCs. A recent study has developed micellar nanoparticles for the delivery of NSC in colorectal cancer suppression. Based on this experiment, self-assembled polymeric micelles were modified with CD44v6 ligand and then, NSC was loaded into nanostructures. The colorectal cancer cells with CD44v6 overexpression had high stemness characteristics that are due to the upregulation of factors such as CXCR4 and ALDH1A, and they demonstrated high sphere formation capacities. The micelles showed high encapsulation efficiency, as much as 93.7 % and they were internalized in HCT116 cells for targeted delivery of NSC. The in vivo experiment on mice revealed that intravenous injection of NSC-loaded micelles significantly reduced the number of circulating tumor cells [41].

The polymeric micelles modified with HDLDBC-bMPA and HDLDBC-bGMPA have been developed for the co-delivery of CP and chloroquine in the treatment of cervical and lung cancers. This combination exerted a synergistic impact and improved the potential of anti-tumor agents in apoptosis induction and cell cycle arrest, and all of them were boosted using micellar nanostructures [42]. Taking everything together, it appears that drug resistance is an increasing challenge in cancer therapy [43,44], and using micelles as nanocarriers is highly recommended to boost the potential of anti-tumor agents.

The internalization of anti-cancer agents is significantly enhanced by micelles, and this increased cellular uptake is one of the factors responsible for boosted efficacy of anti-tumor agents. The micelles have high stability and enhance the half-life of anti-cancer agents. Furthermore, micelles promote blood circulation of anti-cancer agents and, by providing sustained release, achieve complete eradication of tumor cells. The micelles can provide a nano platform for the co-delivery of anti-cancer agents, and their selectivity towards tumor cells can be improved via surface modification, for instance, by folic acid (FA). Besides, micelles are important for preventing drug resistance in cancer, and their distribution seems to be higher in tumor tissues compared to normal tissues [45–55]. A potential reason for the application of micelles in cancer drug delivery is the high biosafety and biocompatibility of these structures, further improving their future clinical application. In addition, the micelles have favorable biodistribution, and they can mainly accumulate in the tumor site. Further functionalization increases their cancer-targeting specificity. Since the micelles have a small size, they can also be encapsulated by other nanocarriers such as liposomes. Moreover, along with drug delivery, other nanoparticles, such as gold and iron oxide nanoparticles, can be loaded in micelles to provide drug delivery and phototherapy in acceleration tumor ablation.

3.2. *Delivery of natural products*

The most important challenge of naturally occurring compounds is their low bioavailability, which restricts their therapeutic index. Curcumin is a phytochemical with anti-cancer activity and the capacity for apoptosis induction, cell cycle arrest, and migration inhibition. However, nanostructures are vital for improving the anti-cancer activity of curcumin. The micelles have been developed for curcumin delivery in cancer treatment. A recent experiment prepared polymeric micelles from HPMA-Bz via nanoprecipitation method, and curcumin was loaded on micellar nanostructures. The curcumin-loaded micelles showed particle sizes of 38, 48 and 59 nm with an encapsulation efficiency of 90 %, 91 % and 94 %. The curcumin release from micelles occurred after 24 h at a level of 22–49 %. The curcumin-loaded micelles induced cell death in tumor cells. The in vivo experiment on mice revealed enhanced half-life of curcumin after intravenous administration and showed high stability. Noteworthy, low bioavailability and high clearance of curcumin from blood are attributed to the interaction of curcumin and blood cells, and based on the function of micelles in enhancing curcumin bioavailability, it can be concluded that micelles reduce the interaction of curcumin with blood cells [56]. Another study has prepared reversible disulfide crosslinked micelles from mPEG-PLA-LA_4 for curcumin delivery in colon cancer suppression. The prepared micelles had a particle size of 24.6 nm with a spherical shape. The micelles promoted the bioavailability of curcumin and maintained its levels in blood circulation. The enhanced accumulation of curcumin at the tumor site by micelles led to colon cancer inhibition, and it exerted a synergistic impact with anti-PD-1 antibody in cancer immunotherapy [57]. Curcumin has the ability to regulate other cell death mechanisms, including ferroptosis [58], autophagy [59], and immunogenic cell death [60]. These pathways can be related to immunotherapy, which is a potential strategy in cancer suppression. Therefore, the role of curcumin-loaded micelles in the regulation of cell death pathways for improving cancer immunotherapy in human cancers should be evaluated.

Another study evaluated the potential of curcumin-loaded micelles in breast cancer therapy. The micellar nanostructures were prepared from mPEG-PCL deblock copolymers via the nanoprecipitation method. The curcumin-loaded micelles had a particle size of 81 nm with a zeta potential of −11.5 mV, showing their high biocompatibility. The micelles had a loading efficiency of 20.65 % and encapsulation efficiency

of 89.32 %, making them appropriate options in cancer drug delivery. The plasma level of curcumin was significantly increased after delivery by micelles by 52.8, 4.63, and 7.51-fold compared to curcumin solution. The in vivo experiment revealed enhanced blood circulation of curcumin and its increased therapeutic index in breast cancer suppression [61]. In another attempt, curcumin was conjugated to starch via an acid-labile ester linker, and then, they were self-assembled into micelles. The micelles had a particle size of 69.1 nm with a zeta potential of −27.8 mV, showing their high stability. These micelles improved the bioavailability of curcumin, and this was responsible for their increased cytotoxicity against tumor cells [62]. Although the studies have mentioned the potential of micelles in improving the pharmacokinetic profile of curcumin in cancer therapy, the underlying molecular pathways have been ignored. Curcumin has a pleiotropic function in the regulation of molecular pathways, including PTEN, PI3K/Akt, non-coding RNAs, and other major pathways that their regulation by micelles, and the changes should be highlighted.

The interesting point is that natural compound-loaded micelles are capable of inducing cell death in drug-resistant cancer cells and suppressing their progression. Quercetin is a naturally occurring compound that can suppress the progression of breast and ovarian tumor cells. An experiment has prepared polymeric micelles from Pluronic polymers, P123 and P407, and P407 and TPGS via the thin film hydration method. The resulting quercetin-loaded micelles demonstrated a particle size of 37 nm, drug loading efficiency of 8.75 %, and encapsulation efficiency of as much as 87.48 %. The micelles enhanced the solubility of quercetin and provided prolonged release. The micelles were stable, and they suppressed tumor progression. Noteworthy, the progression of drug-resistant cancer cells was also suppressed by quercetin-loaded micelles [63]. Based on these studies, naturally occurring compounds are effective in cancer treatment in vitro; however, their potential decreases in vivo, and their half-life and blood circulation time are low. They cannot accumulate in tumor sites, and their internalization in cancer cells is not enough. Therefore, micelles are suggested due to their biocompatibility, stability, and ability to increase intracellular accumulation of anti-tumor compounds (both synthetic and natural agents) (Fig. 8 and Table 2) [64–75]. Such a strategy is also beneficial in clinical studies since the therapeutic efficacy of natural products has been under question due to their pharmacokinetic profile. Regarding the high safety of micelles, they are potential candidates for the delivery of natural products in the treatment of cancer patients.

4. Gene delivery by micelles

The abnormal or dysfunctional genes are responsible for the development of various diseases in humans, and gene therapy is a promising strategy for mediating the proper function of genes. Proper gene therapy appears to be difficult in cancer therapy due to the mild acidic pH of the tumor microenvironment (TME) which can affect the function of genes and the presence of intracellular and extracellular barriers that limit the efficacy of gene therapy. Laser irradiation, electroporation and sonoporation are utilized for cell membrane disruption to enhance the entrance of genes into cells. Furthermore, evasion or suppression of the immune system can be regulated during gene therapy [87]. As there are many limitations for gene therapy for in vivo experiments, including circulation in blood and internalization in cancer cells, nanocarriers have always been under attention to solve aforementioned problems by encapsulating and protecting genes, increasing their internalization in tumor cells and providing long blood circulation. The current section focuses on the function of micelles for the delivery of genes in cancer therapy.

4.1. RNA interference

The process of RNA interference (RNAi) is associated with gene silencing and reduced expression of targeted genes. The most well-known tools employed for RNAi are small interfering RNA (siRNA) and short hairpin RNA (shRNA), and their delivery by micelles is ideal for the purpose of gene therapy and cancer treatment. Most of the experiments have focused on siRNA delivery for the purpose of cancer suppression. However, there are also studies showing that shRNA can be delivered by micelles in cancer treatment. An experiment has prepared polymeric hybrid micelles for the purpose of siRNA delivery in lung cancer treatment. The micelles were prepared using linoleic acid (LA) conjugation to PEI and mPEG, as well as two other amphiphilic polymers, including PEI-LA and mPEG-LA. Then, survivin-siRNA was loaded

Table 1
The surface-modified micelles for targeted cancer therapy.

Nanocarrier	Ligand	Particle size (nm) Zeta potential (mV) Encapsulation efficiency (%)	Cancer type	Remarks	Refs
Polymeric micelles	Folic acid	120 nm 7.7 mV 48 %	Liver cancer	Elimination of 80 % of cancer cells Receptor-mediated endocytosis	[139]
Prodrug micelles	Hyaluronic acid	188 nm −17.54 mV	Lung cancer	Apoptosis induction Receptor-mediated endocytosis	[140]
PCL-PEG/TPGS micelles	d-fructose	38.4 and 57.1 nm	Breast cancer	Internalization via caveolae-dependent, clathrin-independent, and macropinocytosis-independent pathways	[141]
PEO-poly(ester) micelles	P18-4 peptide	52.2 nm	Breast cancer	The enhanced cellular uptake by tumor cells and receptor-mediated endocytosis may be involved in this process	[142]
Dextran-octadecanoic acid micelles	Sialic acid	54.53 nm	Hepatoma	SA-mediated endocytosis to improve internalization in cancer cells	[143]
PEG-PLA micelles	TAT peptide	20 nm +5.94 mV	Breast cancer	The increased internalization in tumor cells shows the role of surface modification with ligands in effective cargo delivery by micelles	[144]
Polymeric micelles	α-Conotoxin ImI	19.3 nm −1.5 mV 98 %	Lung cancer	Preferential accumulation in tumor cells via receptor-mediated endocytosis	[145]
DOCA micelles	Hyaluronic acid	–	Breast cancer	Internalization in tumor cells via CD44 receptor-mediated endocytosis	[146]
TPGS2K/HDP mixed micelles	Folic acid	170 nm −11.81 mV 80 %	Breast cancer	Rapid drug release after endosomal escape and penetration into tumor cells via endocytosis	[147]
TPGS conjugated chitosan micelles	Transferrin	14.83 nm −1.02 mV 86.6 %	Glioma	Enhanced cellular uptake due to receptor-mediated endocytosis	[148]

Table 2
The micellar nanoparticles in delivery of anti-cancer agents.

Nanostructure	Particle size (nm) Zeta potential (mV) Encapsulation efficiency or drug loading (%)	Anti-cancer agent	Cancer type	Remarks	Refs
Folate-targeted polymeric micelles	79.2 nm −8.5 mV 12.6 % (DOX) 1.7 % (SIS3)	Doxorubicin SIS3	Breast cancer	Increased circulation time in blood Preferential accumulation at the tumor site Sensitizing tumor cells to DOX chemotherapy Targeting folate receptor	[76]
β-cyclodextrin-grafted micelles	34.5 nm −2.39 mV Near to 100 % for both drugs	Doxorubicin Conferone	Breast cancer	Exerting synergetic impact Apoptosis induction via the intrinsic pathway	[55]
Prodrug micelles	110.5 nm 55.8 %	Paclitaxel Doxorubicin	Breast cancer	High stability Enhanced cellular uptake High biocompatibility Increased cytotoxicity	[74]
Folate-modified micelles	10–200 nm −20.5 mV Up to 97 %	Metformin Paclitaxel	Breast cancer	Improving cytotoxicity against cancer cells and increased cellular uptake in tumor cells	[77]
Micelles	85.3 nm 96.9 % (silibinin) 97.6 % (docetaxel	Docetaxel Silibinin	Breast cancer	Increased stability in blood circulation and releasing drugs at the tumor site High cellular uptake and biocompatibility Enhanced cytotoxicity	[78]
Self-assembled micelles	278.6 nm +41.6 mV 96 % (wogonin) 52 % (rapamycin)	Rapamycin Wogonin	Breast cancer	Prolonged release of wogonin Increased sensitivity to rapamycin High biocompatibility and stability	[79]
Soluplus/TPGS mixed micelles	63.73 nm −1.26 mV Up to 95.8 %	Docetaxel Piperine	Liver cancer	Synergistic impact and suppressing tumor progression in vitro and in vivo	[80]
Polymeric micelles	55 nm −2.7 mV 87 % (methotrexate) 86.5 % (chrysin)	Methotrexate Chrysin	Breast cancer	Improved performance of chemotherapeutic agents Suppressing tumor progression in vitro and in vivo	[81]
Micellar nanoparticles	519.7 nm	Doxorubicin Wortmannin	Breast cancer	Increased tumor uptake and suppressing cancer progression in vitro and in vivo	[82]
Polymeric micelles	129.8 and 118.6 nm 12 mV	Paclitaxel Disulfiram	Breast cancer	Suppressing drug resistance and reducing the viability of tumor cells	[83]
Copolymer micelles	122 nm −16.3 mV 82 %	Paclitaxel *trans*-retinoic acid	Lung cancer	Preventing tumor growth in vivo and enhancing survival of animal models	[84]
Polymeric micelles	41–44 nm 99.5 %	Paclitaxel Honokiol	Breast cancer	Reducing the expression level of P-gp Inhibiting migration and invasion in vivo Drug release at the tumor site	[85]
Polymeric micelles	80–90 %	Paclitaxel Cisplatin	Breast and ovarian cancers	Improving cytotoxicity against tumor cells	[86]

on self-assembled polymeric micelles for targeted delivery to lung cancer cells. Due to the enhanced uptake of siRNA in tumor cells, a remarkable reduction was observed in the expression level of the survivin gene to suppress cancer proliferation and sensitize them to cell death [88]. Based on the function of genes, they can be targeted by related siRNAs loaded in micelles. Breast CSCs rely on the upregulation of the AKT2 gene. Hence, developing AKT2-siRNA can suppress the progression of breast CSCs. For this purpose, polymeric micelles were prepared using Pluronic F127 and polyplexes. Then, AKT2-siRNA conjugated with cationic PEI was attached to micelles. Two kinds of breast cancer cells, including MCF-7and MDA-MB-231 cells, were chosen, and they were exposed to AKT2-siRNA-loaded polymeric micelles; the results showed that siRNA-loaded micelles have a capacity to reduce AKT2 gene expression to impair stemness of breast cancer and decrease their proliferation and invasion [89].

The application of micelles for siRNA delivery has made it possible to obtain promising results in vivo, while naked siRNA has low capacity in animal models. An experiment prepared polymeric micelles from PEG-b-PLL and then modified them with cRGD peptide. The resulting micelles had siRNA-binding segments containing thiol. The siRNA-loaded polymeric micelles were used for the treatment of cervical cancer. The micelles had different particle sizes, and the largest size was 194 nm with a zeta potential of −1.99 mV. The cRGD-modified siRNA-loaded polymeric micelles effectively decreased gene expression in vitro, and due to their modification with cRGD peptide, they showed high cellular uptake and internalization in cervical cancer cells that are of importance for improving gene silencing capacity. After intravenous injection in animal models, siRNA-loaded polymeric micelles showed high stability in blood circulation, and they preferentially accumulated in tumor tissues to suppress the progression of cervical cancer [90].

As siRNA has an anionic nature, micelles should have a positive charge for conjugation with these nucleic acid drugs. A recent study conjugated cationic PEI to PEG-conjugated VEGF-siRNA to suppress the progression of prostate cancer. The siRNA-loaded polymeric micelles demonstrated a particle size of less than 100 nm, and they showed high biocompatibility, as they did not induce any detectable immune response in animal models. The siRNA-loaded polymeric micelles accumulated in tumor tissues, and they were able to suppress cancer growth in vivo upon intravenous and intertumoral administration (Fig. 3) [91]. The modification of micelles with polymers can affect their capacity for siRNA delivery. For this purpose, a study prepared polymeric micelles from PEG-b-pDPB and pD-b-pDPB, and then, the effect of PEGylation on the capacity of micelles for siRNA delivery was evaluated. It was found that modification of micelles with low molecular weight PEG reduces internalization in breast tumor cells, but it mediates endosomal escape and promotes cytoplasmic bioavailability. On the other hand, modification of micelles with high molecular weight PEG improves blood circulation time [92]. Based on these studies, it appears

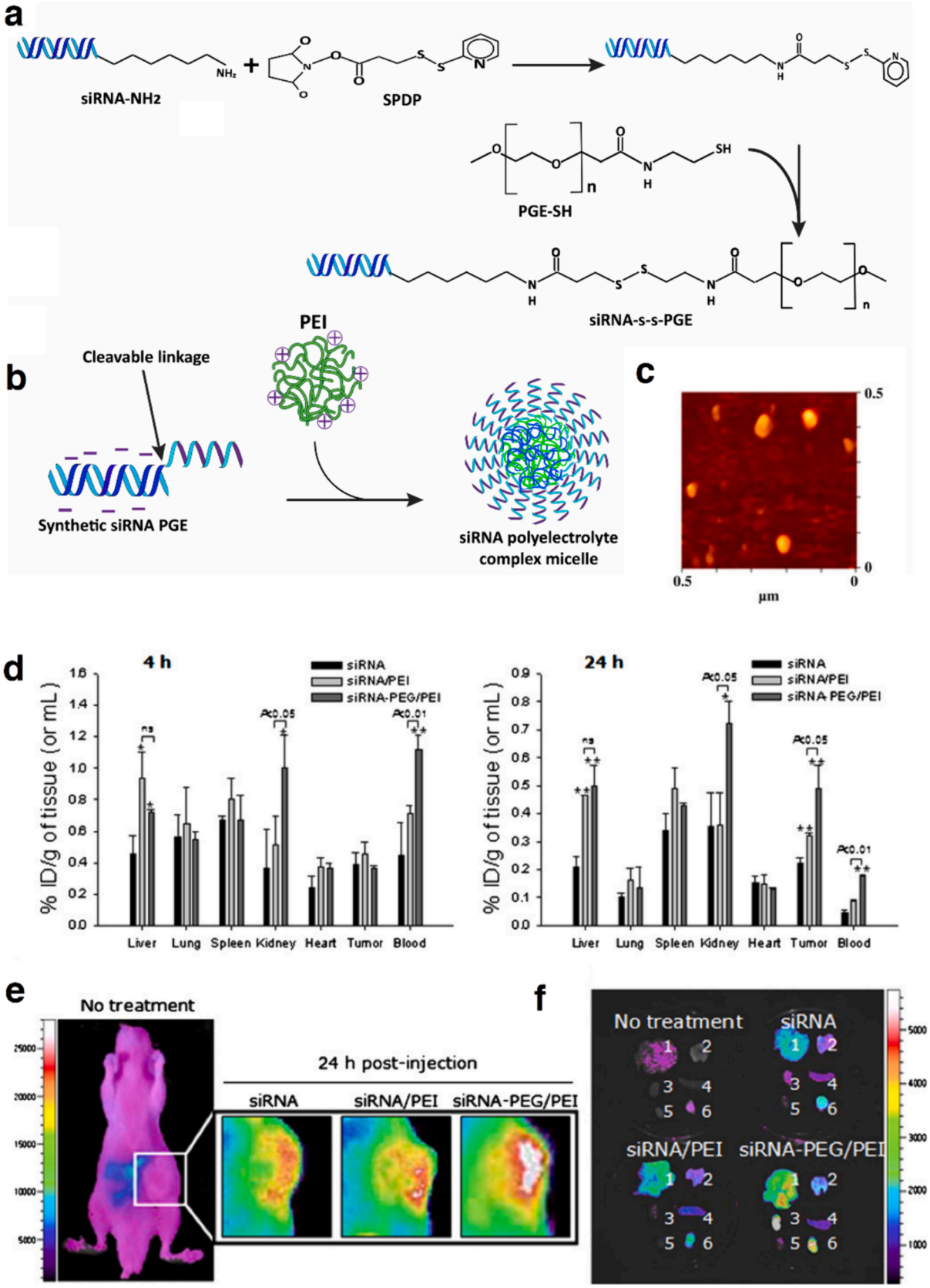

Fig. 3. (a-c) Preparation of siRNA-loaded micelles with a cleavable bond, (d-f) Biodistribution of micelles at targeted tissue. Reprinted with permission from [91] from Elsevier.

that micelles are able to enhance the impact of siRNA in gene silencing in vitro and in vivo, and it is of importance for suppressing cancer progression [93–95]. Similar results have been obtained for shRNA, showing that micelles are capable of increasing intracellular uptake and efficiency of shRNA in gene silencing. However, studies are limited, and more experiments are required in this case to show the true potential of micelles in shRNA delivery and gene silencing for the purpose of cancer treatment (Fig. 4) [96]. Regarding the negative charge of siRNA, loading these genetic tools in polymeric micelles with a positive charge is suggested to develop stable complexes in cancer gene therapy.

4.2. Non-coding RNA

The non-coding RNAs (ncRNAs) comprise a large part of the human genome, and they have received much attention in recent years due to their regulatory roles in biological events and their capacity to affect proliferation, migration, angiogenesis, and differentiation in normal cells. The role of ncRNAs in cancer can be tumor-suppressor and oncogene, and based on their function, the expression level of these factors changes in tumor progression. The microRNAs (miRNAs) are the most well-known members of ncRNAs, and they obtain their function in the cytoplasm by embedding into an RNA-induced silencing complex (RISC). The miRNAs reduce the expression of target genes by binding to 3́-UTR region of the target. There have been efforts for the delivery of miRNAs by micelles in cancer therapy. An experiment applied micelles for miRNA-34a and BI6727 as PLK1 inhibitors in the treatment of pancreatic cancer. The self-assembled polymeric micelles were prepared from PEG-B-PAEBEA, and they had a particle size of 100 nm, drug loading efficiency of 100 %, and can provide a stable complex of miRNA-34a and micelles. The in vitro and in vivo (systemic administration) experiments revealed the potential of micelles in promoting the efficacy of miRNA-34a and volasertib in cancer suppression, increasing plasma levels and accumulation at the tumor site. The results showed that a combination of miRNA-34a and volasertib exerts synergistic tumor-suppressor activity in reducing the progression of pancreatic cancer cells and is able to induce G2/M arrest and prevent colony formation

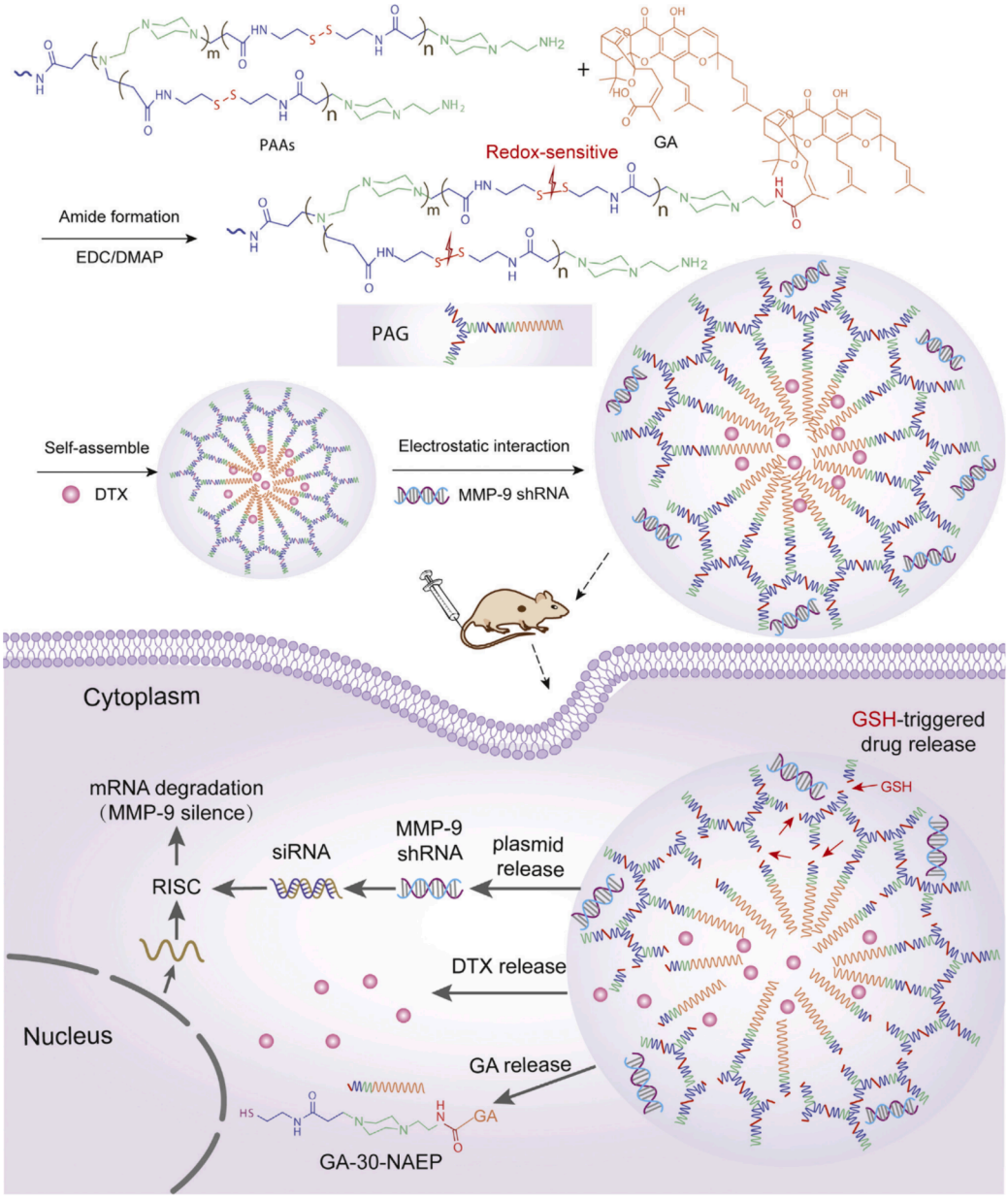

Fig. 4. Preparation of micelles and their entrance into tumor cells to release MMP-9-shRNA and DTX for a combination of chemotherapy and gene therapy. Reprinted with permission from [96] from Elsevier.

capacity of pancreatic cancer cells [97]. Another study has developed polymeric hybrid micelles for miRNA-34a and irinotecan delivery in colorectal cancer suppression. The irinotecan is a suppressor of topoisomerase enzymes and is beneficial in preventing the replication of colorectal cancer cells. The DSPE-PEG and PEI-PLA polymers were used for developing polymeric micelles and then, irinotecan and miRNA-34a were loaded on micelles. The resulting polymeric hybrid nanostructures had a particle size of 170–200 nm, a zeta potential of −11.65 mV, and an encapsulation efficiency of as much as 91 %. The miRNA-34a release from micelles in colorectal cancer cells leads to a significant decrease in growth and metastasis and affects expression levels of Bcl-2 and mTOR pathways. Then, the way is paved for irinotecan to exert its tumor-suppressor activity [98]. Furthermore, miRNA-34a-loaded micelles sensitize prostate cancer cells to chemotherapy [99].

The miRNA-205 is another factor loaded on micelles for the treatment of pancreatic cancer. For this purpose, cationic polymeric micelles were prepared from mPEG and PCC and then, they were used for delivery of miRNA-205 and gemcitabine. The resulting nanocarriers had a particle size of 62.1 nm and a zeta potential of 14.15 mV. These nanocarriers released cargo in a prolonged manner and for more than 10 days. They demonstrated transfection efficiency of more than 90 % and promoted stability of miRNA in serum. These improvements, along with an increase in cellular uptake, led to a significant decrease in the progression of pancreatic cancer cells [100]. Therefore, micelles are promising nanocarriers for the delivery of miRNAs in cancer therapy [98], and future experiments should focus on the delivery of lncRNAs and circRNAs by micelles in cancer suppression. Figs. 5–7 provides a schematic representation of micelles for gene delivery.

In addition to siRNA and non-coding RNAs, there are also other factors that contribute to the genetic modulation of cancer such as shRNA and CRISPR/Cas9 system. Regarding shRNA, the mechanism of action is similar to siRNA, and therefore, the same result can be obtained. However, CRISPR has the ability to both downregulate and upregulate targeted genes (siRNA can only downregulate gene expression), and it is a better system for cancer therapy. However, CRISPR/Cas9 size is high, and it may affect further biological effects of micelles, including their cellular internalization, blood circulation, and phagocytosis by the reticuloendothelial system.

5. Cargo co-delivery: Gene and drug

In order to maximize the potential for cancer suppression, micellar nanoparticles have been developed for the co-delivery of genes and drugs. Recently, anionic dextran-coated micelles were designed for the delivery of camptothecin and survivin-shRNA in colon cancer therapy. The selectivity of micelles towards colon cancer cells was improved via AS1411 aptamer modification. The modification of micelles with dextran is beneficial in decreasing particle size by preventing aggregation. After dextran modification, the particle size of micelles was decreased from 160 nm to 131 nm. However, aptamer modification enhanced size to 235 nm, and zeta potential was –22 mV. The drug- and shRNA-loaded micelles penetrated into colon cancer cells via endocytosis, and by mediating survivin down-regulation, apoptosis (38 %) occurred, and cancer cells were sensitized to chemotherapy [101]. However, as genes have an anionic charge, it is suggested to synthesize cationic nanostructures to provide a stable complex. In an effort, pullulan was used for the synthesis of cationic micelles, and lipophilic deoxycholic acid and PEI were grafted into the backbone of pullulan. The resulting nanocarriers had a particle size of 160.8 nm, a zeta potential of 28 mV, with an encapsulation efficiency of 84.05 %. Then, DOX and *p53* genes were loaded on micelles for breast cancer therapy. It was found that micelles provide prolonged delivery of DOX, which improves its anti-tumor activity. Furthermore, *p53* gene delivery induces apoptosis in cancer cells and sensitizes breast tumor cells to DOX

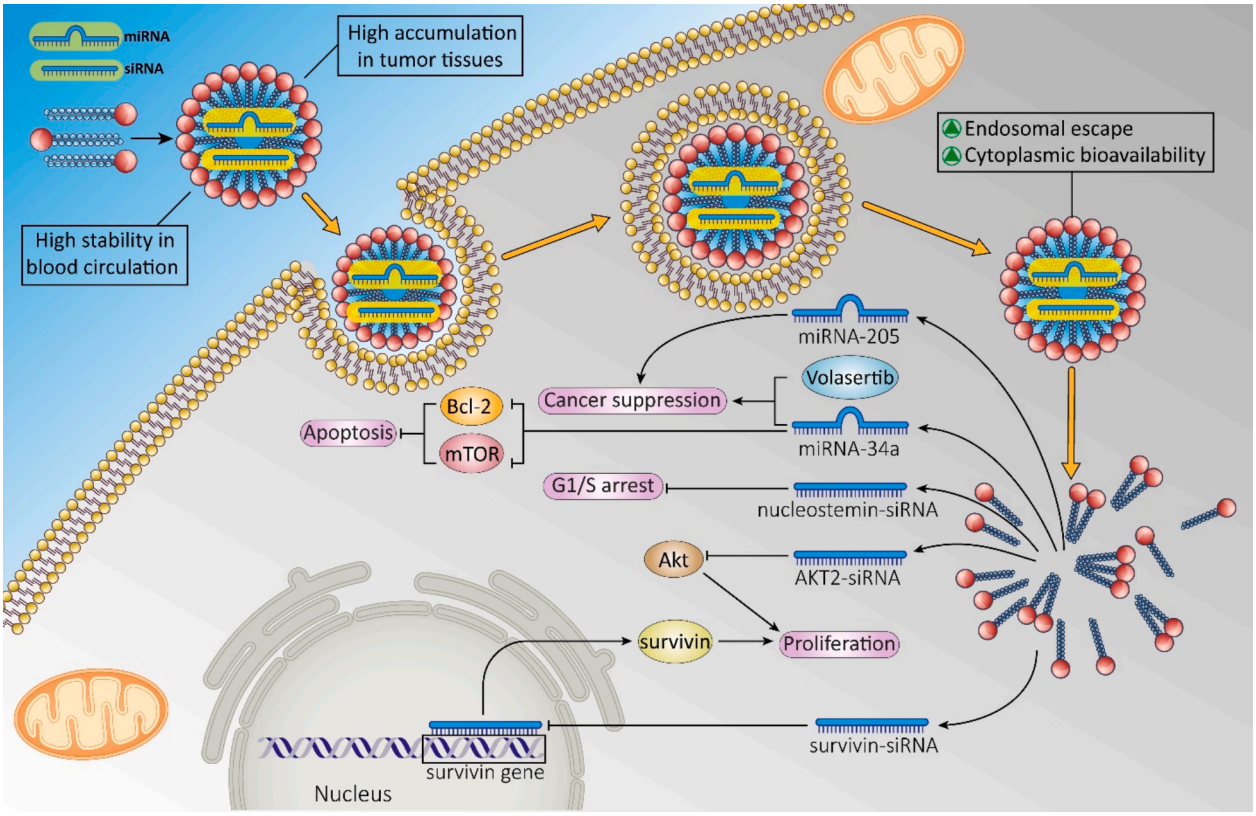

Fig. 5. Micelles for the purpose of gene delivery. The micelles provide cytoplasmic release of genes after entrance into cells and endosomal escape to affect gene expression in the nucleus in regulating proliferation, apoptosis, and cell cycle progression in tumor cells. Several underlying molecular pathways are targeted by these micelles in cancer therapy, including Bcl-2, mTOR, Akt, and survivin, to impair the survival of tumors.

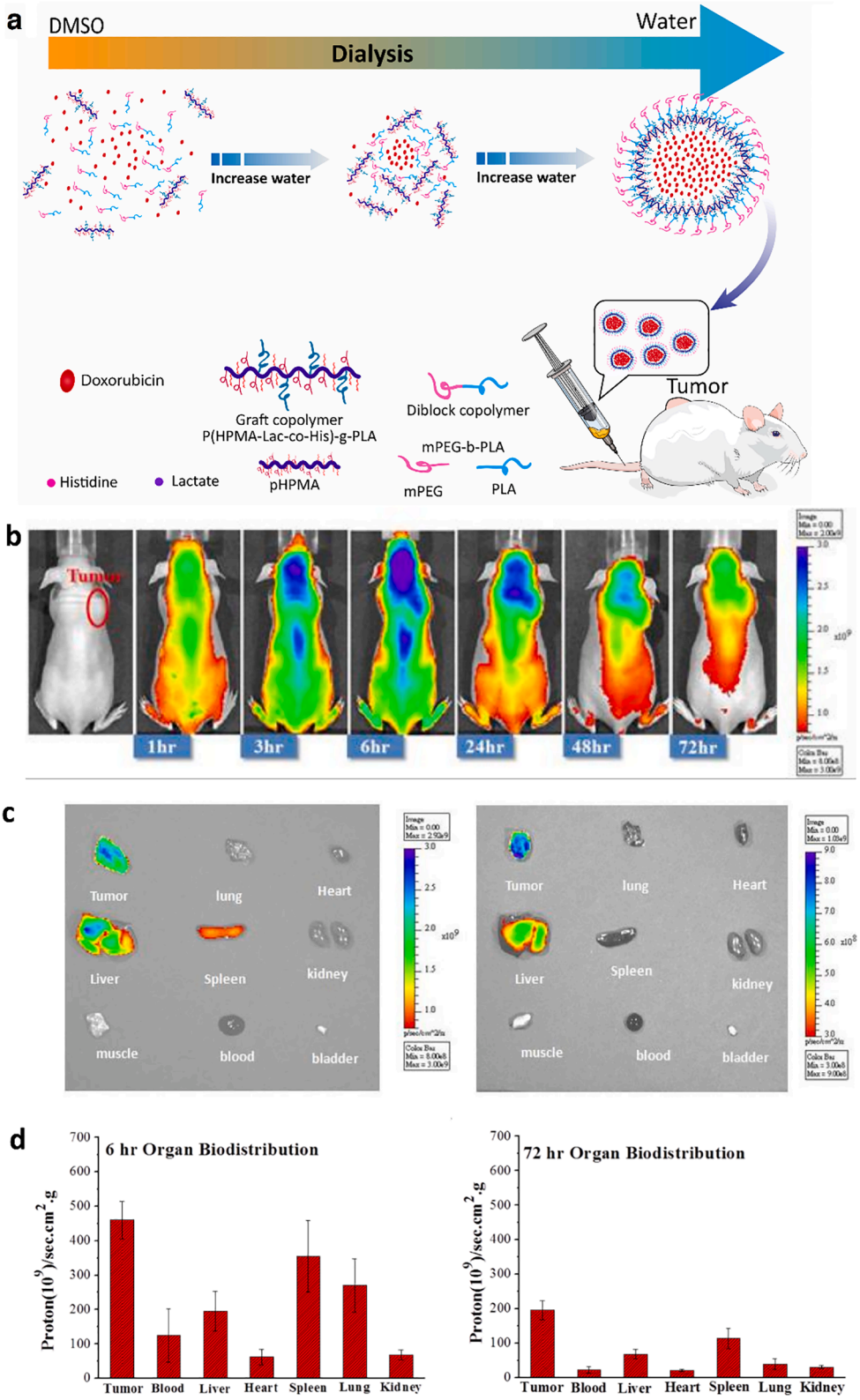

Fig. 6. (a) The preparation of polymeric micelles from mPEG-b-PLA polymers and their anti-cancer activity. (b) and (c) The biodistribution of micelles and their accumulation in tumor tissue. (d) The highest accumulation of micelles was observed in tumor tissue after 6 h, and then their accumulation decreased after 72 h. After tumor tissue, the highest accumulation of micelles was observed in the kidney. Reprinted with permission from [38] from MDPI.

chemotherapy [85]. As micelles have a capacity for miRNA delivery [86], further studies can show how the co-delivery of miRNAs and drugs by micelles can be beneficial in combination cancer therapy.

Noteworthy, most of the experiments have focused on the co-delivery of drugs and siRNA in synergistic cancer therapy [102]. As discussed in the previous section, PLK1 overexpression significantly enhances the progression of tumor cells. Co-delivery of DOX and PLK1-siRNA appears to be beneficial in breast cancer treatment and reducing

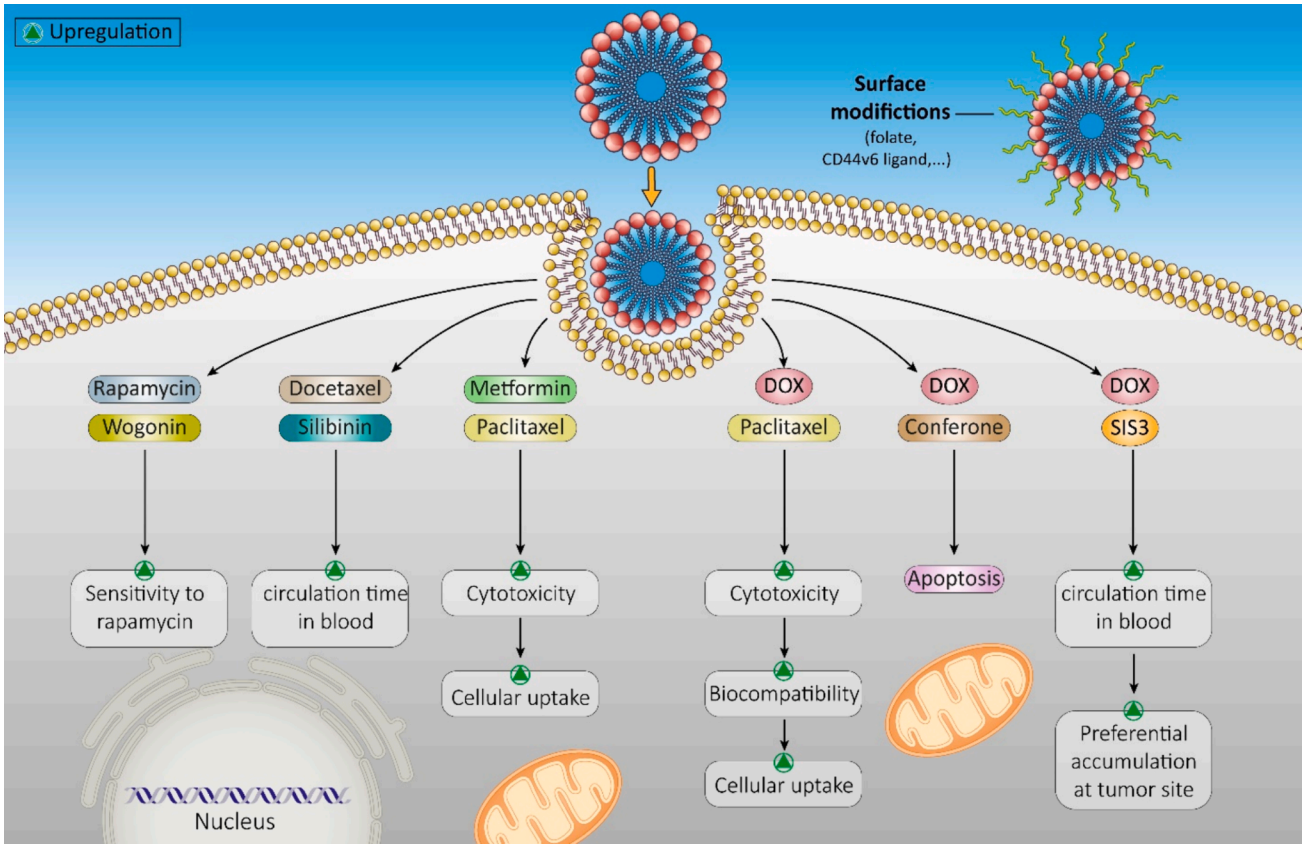

Fig. 7. Micelles for the purpose of drug delivery. Both synthetic and phytochemicals can be delivered by micelles in cancer therapy to enhance biocompatibility, promote intracellular accumulation, provide combination cancer therapy, and prevent drug resistance development.

its progression [103]. Another study also focused on the delivery of DOX and PLK1-siRNA using micelles, and in this case, polymeric micelles were prepared from poly(styrene-alt-maleic anhydride), and then, DOX and siRNA were loaded. The resulting micelles had a particle size of 14–30 nm, and they localized in the cytoplasm of breast tumor cells, leading to a significant decrease in the proliferation rate of tumor cells [104]. In addition to synthetic drugs, micelles have been applied in the co-delivery of curcumin and siRNA. The self-assembled micelles were prepared from chitosan and cholesterol. The resulting nanostructures had a particle size of 165 nm with a zeta potential of + 24.8 mV. The micelles were penetrated into lung tumor cells via clathrin-mediated endocytosis, and they were stable for more than one month at 4 °C. Therefore, they can be considered as promising nanocarriers in lung tumor therapy [105]. Similar to DOX, PTX resistance is an increasing challenge and delivery systems are of importance for boosting its anti-tumor activity. The overexpression of survivin stimulates PTX resistance in ovarian tumor cells. The multifunctional micelles loaded with survivin-siRNA and PTX sensitize ovarian tumors to cell death [106]. Based on the experiments, it appears that micelles can provide stable platforms for the co-delivery of genes and drugs, and their clinical application should be considered in the next steps [53,107–111]. Table 3 provides a summary of micelles for co-delivery of genes and drugs in cancer therapy.

6. Functionalized micelles: Boosting cell internalization

A newly emerging field in improving the selectivity of nano-scale delivery systems is to identify receptors overexpressed on the surface of cancer cells and then find an antibody capable of binding to the receptors. Then, surface modification of nanostructures with ligands can be performed to design receptor-targeted nanocarriers. For instance, CD44 shows overexpression on the surface of most tumor cells, such as breast and lung cancer cells. Hyaluronic acid (HA) has the capacity to bind to CD44 receptors, and surface modification of nanostructures with HA mediates selective targeting of cancer cells overexpressing CD44. The same strategy has been employed to increase the selectivity of micelles towards cancer cells. The glioblastoma multiform is one of the most malignant brain tumors, and various anti-cancer agents, including gemcitabine and honokiol, have been employed for its treatment. However, the drugs should cross over BBB to enter into the brain and reach the tumor site. An experiment has prepared micelles for the co-delivery of honokiol and lauroyl-gemcitabine in glioblastoma therapy. The drug-loaded micelles were modified with HA to improve their selectivity. The in vitro and in vivo studies revealed that drug-loaded micelles suppress colony formation of glioblastoma cells, and nanocarriers promote the anti-tumor activity of honokiol and gemcitabine. The drug-loaded micelles reduced tumor volume in mice and enhanced the survival of animal models. Proliferation inhibition and apoptosis induction are followed by drug-loaded micelles in suppressing glioblastoma progression. Notably, surface modification of micelles with HA led to selective targeting of glioblastoma cells overexpressing CD44 receptors and subsequent internalization in tumor cells via receptor-mediated endocytosis [116]. Another study synthesized cationic micelles from amphiphilic ferrocenium-tetradecyl. Then, micelles were modified with HA that had a particle size of 117 nm with a zeta potential of + 51.8 mV. DOX as an anti-cancer agent was loaded in HA-modified micelles, and drug loading efficiency was 5.97 %. The modification of micelles with HA changed their zeta potential, and it was in the range of −25.7 to −12.3 mV. These DOX-loaded HA-modified micelles effectively suppressed tumor progression in vitro and in vivo and were able to internalize in tumor cells due to targeting CD44 receptors [117]. Hence, surface modification of micelles with HA appears to be a promising

Table 3
The micelles for co-delivery of genes and drugs in cancer therapy.

Nanocarrier	Cargo	Particle size (nm) Zeta potential (mV) Encapsulation efficiency (%)	Cancer type	Remarks	Refs
Micelles	Docetaxel anti-nucleostemin siRNA	42 nm −12.8 to 15 mV	Prostate cancer	Modification with TAT peptide and DCL ligand promotes the selectivity of micelles toward tumor cells Reducing expression level of nucleostemin Proliferation suppression	[112]
Self-assembled micelles	Doxorubicin PLK-1 siRNA	82.2 nm 26.1 mV 8.6 % /w	Breast cancer	Increasing stability of nanocarriers by coating via bovine serum albumin Cargo release in response to pH 5 and GSH Exerting synergistic impact and suppressing tumor progression in vitro and in vivo	[103]
Cholesterol-grafted chitosan micelles	Curcumin siRNA	165 nm 24.8 mV	Lung cancer	The capacity of nanocarriers in condensing siRNA and curcumin High stability and cellular uptake by lung cancer cells Internalization in tumor cells via clathrin-mediated endocytosis	[105]
Tri-layer micelles	Gemcitabine NF-κB siRNA	Up to 217.3 nm 27.5 mV 99 %	Breast and pancreatic cancers	Enhanced cytotoxicity against tumor cells Reducing NF-κB expression Apoptosis induction and reducing migration of cancer cells	[108]
Dendrimer micelles	Doxorubicin MDR1 siRNA	349.3 nm 6.59 mV	Breast cancer	Surface modification of nanoparticles with 2C5 as a monoclonal antibody results in specific targeting of cell-surface-bound nucleosomes Increased cellular uptake and suppressing tumor progression in vitro and in vivo	[109]
LDL-coupled micelles	Paclitaxel siRNA	24.36 nm −1.34 mV	Breast cancer	Increased cargo release at mild acidic pH Lysosomal escape of nanoparticles via proton sponge effect Synergistic impact between gene and chemotherapy	[113]
Chitosan-coated micelles	Paclitaxel MDR1 siRNA	171.6 nm 93.92 %	Breast cancer	Increased cellular uptake due to LDL modification and binding to receptors on cell surface Protection of siRNA against phagocytosis degradation Reducing MDR1 expression and down-regulating P-gp expression Suppressing tumor growth in vitro and in vivo	[114]
Self-assembled micelles	Narciclasine ULK1 siRNA	99 nm 28.5 mV	Hepatocellular carcinoma	Cargo release at tumor microenvironment Suppressing protective autophagy Apoptosis induction and decreasing proliferation rate	[115]
Polymeric micelles	Docetaxel MMP-9 shRNA	163.5 nm 22.7 mV	Breast cancer	Release of the drug at the tumor site Suppressing the growth rate of tumor cells Increasing cellular uptake	[96]

strategy for boosting tumor suppression capacity [118].

It is worth mentioning that the interaction between cell surface receptors and their ligand can stimulate the progression of tumor cells (both proliferation and metastasis). Therefore, surface modification of micelles with ligands not only promotes selectivity but also prevents cancer cell progression. A new experiment has shown that modification of micelles with MCP-1 peptide can target CCR2-overexpressed cancer cells. Furthermore, micelles were conjugated with KLAKLAK to induce apoptosis in tumor cells. These micelles had a particle size of 12–14 nm with zeta potential up to 16.2 mV. The MCP-1-modified micelles interacted with CCR2 on the surface of melanoma cells. The KLAK peptide was able to stimulate cell death, and in vivo experiments revealed a significant decrease in cancer progression up to 34 % after intravenous administration of micelles. Furthermore, after the interaction of MCP-1-modified micelles with the CCR2 receptor, the infiltration of tumor-associated macrophages and cytotoxic T lymphocytes in TME showed an alteration, confirming the dual function of targeting receptors [119].

Another kind of ligand that can be employed for surface modification of micelles is aptamers. As single-stranded oligonucleotides, aptamers are produced via the SELEX method, and they have a high affinity towards their targets that is of importance for enhanced internalization [120]. A recent study has developed polydiacetylene micelles via click and hybridization method and their surface modification with aptamer (anti-Annexin A2 sequence) has been performed. This modification significantly promoted intracellular accumulation of micelles in breast cancer cells [121]. Such a strategy is beneficial in elevating the anti-tumor activity of drugs. The DOX-loaded polymeric micelles were synthesized for pancreatic cancer therapy, and they had a particle size of 132.9 nm, encapsulation efficiency of 60 %, drug loading efficiency of 18.11 %, and zeta potential of −24.45 mV and –33.30 mV. The XQ-2d aptamer was used to modify DOX-loaded polymeric micelles, and results showed that aptamer modification is associated with deep tumor penetration and subsequent increase in cytotoxicity of DOX against pancreatic cancer cells [122].

As mentioned in previous sections, nanostructures are beneficial in improving the bioavailability and anti-tumor activity of natural compounds. The polymeric micelles were prepared from methoxy-polyethylene glycol-poly(d,l-lactide), and then curcumin was loaded on nanocarriers. At the next step, modification of micellar nanostructures with transferrin (Tf) was performed. The Tf-modified curcumin-loaded micelles had a particle size of 132.16 nm and an encapsulation efficiency of 88.27 %. The micelles provided prolonged release of curcumin, improving its anti-tumor activity, and it was found that Tf-modified micelles have higher cellular uptake compared to non-targeted micelles in liver and cervical cancer cells. The potential of curcumin in apoptosis induction and reducing colony formation increased by Tf-modified micelles [123]. Another experiment also modified vitamin E/lipid-based polymeric micelles with Tf with a particle size of 114.2 nm and zeta potential of –22.8 mV. Similarly, Tf-modified micelles showed high internalization in cervical and liver cancer cells, and these stable nanocarriers elevated the anti-tumor activity of curcumin [123]. Taking everything into account, it appears that micelles have the capacity for cancer suppression via cargo delivery, and they boost the efficacy of anti-cancer drugs. They are stable and have a great safety profile. The current section revealed that surface modification of micelles is another approach to improving the potential of micelles in cargo delivery, increasing cellular uptake, and decreasing tumor growth in vitro and in vivo [47,124–128].

When the modification of nanostructures occurs, their internalization in cancer cells changes. In previous sections, it was shown that micelles can internalize in tumor cells. The most important pathway for micelles to enter tumor cells is endocytosis. A recent experiment has

produced self-assembled micelles from heparosan and deoxycholic acid conjugates (HSDs) for delivery of DOX. The micelles significantly enhanced the accumulation of DOX in cancer cells, and it was found that micelles penetrate into laryngopharyngeal cancer cells via clathrin-mediated endocytosis that is energy-dependent (Fig. 2) [129].

The surface-modified micelles can enter cancer cells via receptor-mediated endocytosis [131]. For instance, it has been shown that HA-modified curcumin-loaded micelles penetrate cancer cells via CD44-mediated endocytosis [132]. It appears that all kinds of endocytic mechanisms can participate in the intracellular uptake of micelles in tumor cells, but the role of some of them is more prominent. It has been reported that heparosan polysaccharide-based micelles are promising carriers for DOX delivery in various cancers (breast, lung, melanoma, and gastric cancers). It was found that these micelles mainly penetrate cancer cells via clathrin-mediated endocytosis and macropinocytosis, while other pathways, including micropinocytosis, clathrin-mediated endocytosis and clathrin/caveolae-mediated endocytosis also contribute to the penetration of micelles in tumor cells [133]. The surface modification of micelles with folate leads to their internalization in cancer cells via receptor-mediated endocytosis [134,135]. Based on these experiments, it can be concluded that micelles have the capacity to enter into cancer cells via endocytosis, and when they are modified with ligands, their internalization occurs via receptor-mediated endocytosis [136–138]. Table 1 provides a summary of micelle internalization into tumor cells via endocytosis.

7. Immunotherapy

The field of cancer immunotherapy appears to have started in the 1950s when specific tumor antigen was reported using a chemical-induced tumor model [149]. The field of immunotherapy has provided significant promises for the treatment of cancer, especially advanced tumors [150]. Pre-clinical studies have shown the capacity of immunotherapy in cancer suppression, and a high number of clinical studies are currently being performed on cancer immunotherapy [151]. Based on the experiments, it seems that micelles can be employed for cancer immunotherapy. A recent experiment has focused on targeting tumor-associated macrophages (TAMs) present in TAM for the purpose of cancer immunotherapy. The polymeric micelles were prepared from ACP and PPP blocks, and they showed particle size of 117.6 nm and 110.1 nm, zeta potential of −11.3 mV and −28.8 mV, and encapsulation efficiency of 53.4 % for DOX and 63.6 % for R837. The DOX as a chemotherapeutic agent and R837 as an immunomodulator (imiquimod) were loaded on polymeric micelles to suppress cancer progression. After intratumoral and intravenous administration, drug-loaded polymeric micelles suppressed the progression of breast cancer animal models. The released R837 mediated the maturation of TAMs to provide anti-tumor immunity and prevent immunosuppression in breast cancer. The released DOX, induced cell death in breast cancer and provided simultaneous chemo-/ and immuno-therapy [152]. However, it should be mentioned that TAMs have both tumor-suppressor and tumor-promoting functions. It has been reported that TAMs can induce immunosuppression and promote the progression of melanoma cells. The calcium crosslinked polymeric micelles were prepared for intratumoral delivery of M−CSF, and the results revealed that tumor growth in vivo decreases due to anti-tumor immune response mediated by cytotoxic T cells and the capacity of TAMs in immunosuppression is prohibited [153]. This dual function of macrophages emanates from their polarization. Overall, there are two kinds of macrophages: M1 polarized and M2 polarized macrophages. The high levels of M2 macrophages in TME are in favor of tumor progression, while M1 macrophages prevent tumor growth [149,154,155]. A recent study employed self-assembled micelles prepared from DACH-Pt(II) conjugation PKS copolymer to deliver platinum-based drugs in colorectal cancer immuno-/chemo-therapy. The drug-loaded micelles had a particle size of 120 nm and a zeta potential of −16.9 mV. Increasing the length of PKS significantly promotes the drug-loading capacity of polymeric micelles, and they showed biodistribution in tumor tissue. In order to improve the hydrophilicity of micelles, lysine molecules were embedded into micelles, and they provided endosomal escape. These drug-loaded micelles promote levels of reactive oxygen species (ROS) to mediate apoptotic cell death and decrease the expression level of CD47. Furthermore, micelles stimulated M1 polarization of macrophages and provided phagocytosis of tumor cells for cancer immunotherapy (Fig. 8) [156].

The micelles are of importance for improving the efficacy of immunotherapeutic strategies for cancer suppression. The T cell response is induced in cancer immunotherapy, and for this purpose, antigen/adjuvant should reach the tumor site. However, the biodistribution of antigen/adjuvant at the tumor site is poor. The polymeric hybrid micelles were prepared from PCL-PEG and PCL-PEI, and then, Trp2 peptide and CpG oligodeoxynucleotide as adjuvants were loaded on micellar nanoparticles. The micelles demonstrated good properties, including particle size up to 82.45 nm, zeta potential of + 18.23 mV, and encapsulation efficiency of 98 % for Trp2 and CpG. After subcutaneous administration, the CpG/Trp2-loaded micelles accumulated in lymph nodes, and low cytotoxicity was observed towards dendritic cells. They induced activity of cytotoxic T lymphocytes and were beneficial in improving anti-tumor immunity against melanoma [158]. Therefore, it appears that significant progress has been made in introducing immunotherapy for cancer, [159–162] and different checkpoint inhibitors and agents capable of regulating immune cells in TME have been developed. However, there are still problems associated with the delivery of immune treatments and their localization at the tumor site. Hence, the biodistribution of such immunomodulatory compounds should be improved, and due to their safety profile, high loading efficiency, and targeted release at the tumor site, micelles can be considered ideal candidates in this case (Fig. 9). Table 4 provides a summary of micellar nanoparticle application in cancer immunotherapy applications.

8. Stimuli-responsive micelles

Tremendous attention has been received in the field of materials science for imaging, diagnosis, and treatment of different types of cancer in the recent decade [170]. A specific focus has been paid to the design and synthesis of nanoscale materials that are able to increase the anti-cancer drugs' efficiency and targeting. The final goal is to know where and when the nanomaterials are in need throughout the body [171]. An effective strategy to achieve this goal is to utilize stimuli-responsive nanomaterials, which are triggered by different biological signals (endogenous) or external stimuli (exogenous). The external stimuli are light, ultrasound, magnetic field, ultraviolet, etc., and the innate triggers are enzymes, pH, redox, glucose, etc [172]. Among the mentioned stimulators, pH, redox, and light-responsive micelles have been studied more, and so these are covered in this section. Moreover, another subcategory has also been discussed on the multi-responsive micelles in cancer therapy, as this family of micelles is in an ever-increasing development because of their multi-functionality and higher efficiency.

8.1. pH responsive micelles

Biomaterials functionalized with pH-sensitive groups are of particular interest in cancer therapy as they undergo swelling, membrane disruption, and degradation once the change in the pH of their microenvironment has occurred. Generally, the mentioned functionalization groups contain either amine or carboxylic acid. It is worth mentioning that various pH's represent different pathologies and intracellular environments. Once a material undergoes endocytosis, it will experience a gradient pH from nearly neutral to acidic (6–6.8) in the endosomes and even much more in the lysosomes (5) [173]. Moreover, in the case of inflammation and cancer (tumor's site), the local sites have an acidic pH, which is significantly different from a healthy tissue, and this situation provides an opportunity to aim these targets with biomaterials

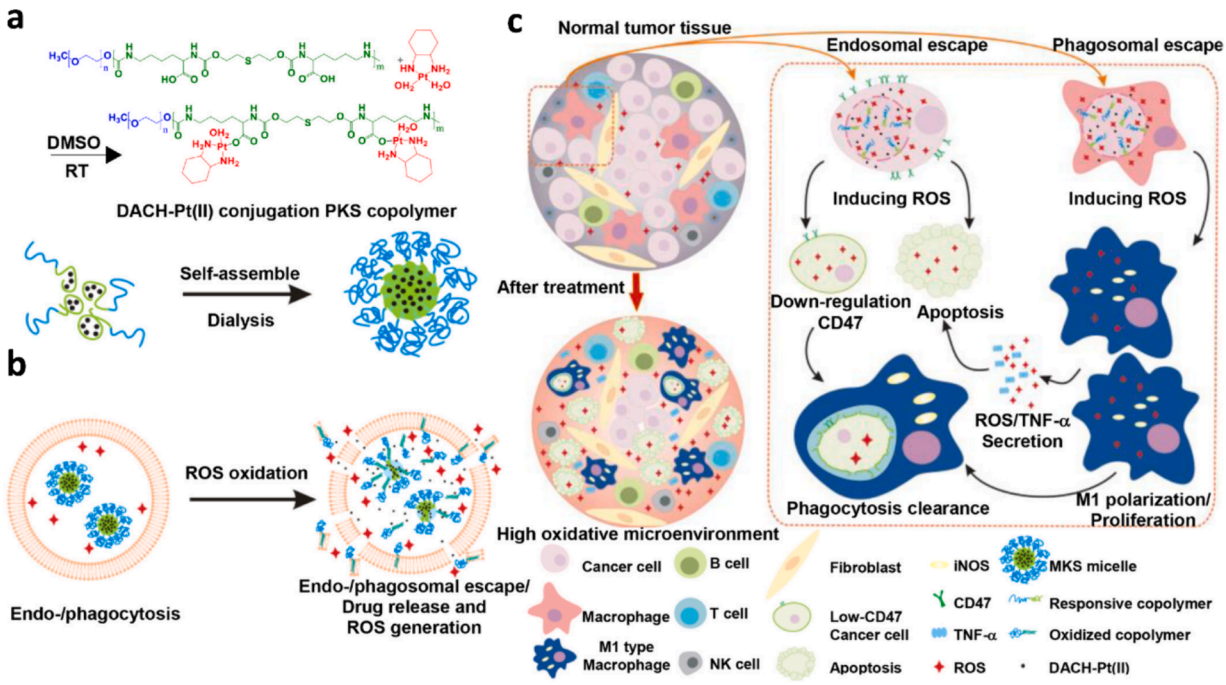

Fig. 8. (a-c) The potential of prepared nanomicelles for regulating TME components is that, in this way, micelles affect the polarization of macrophages to prevent immunosuppression. The self-assembled micelles were prepared from DACH-Pt(II) conjugation PKS copolymer, and in addition to increasing ROS production, they mediate endo-/phagosomal escape. The increase in ROS generation by micelles reduced CD47 expression while it increased apoptosis. Reprinted with permission from [157] from Elsevier.

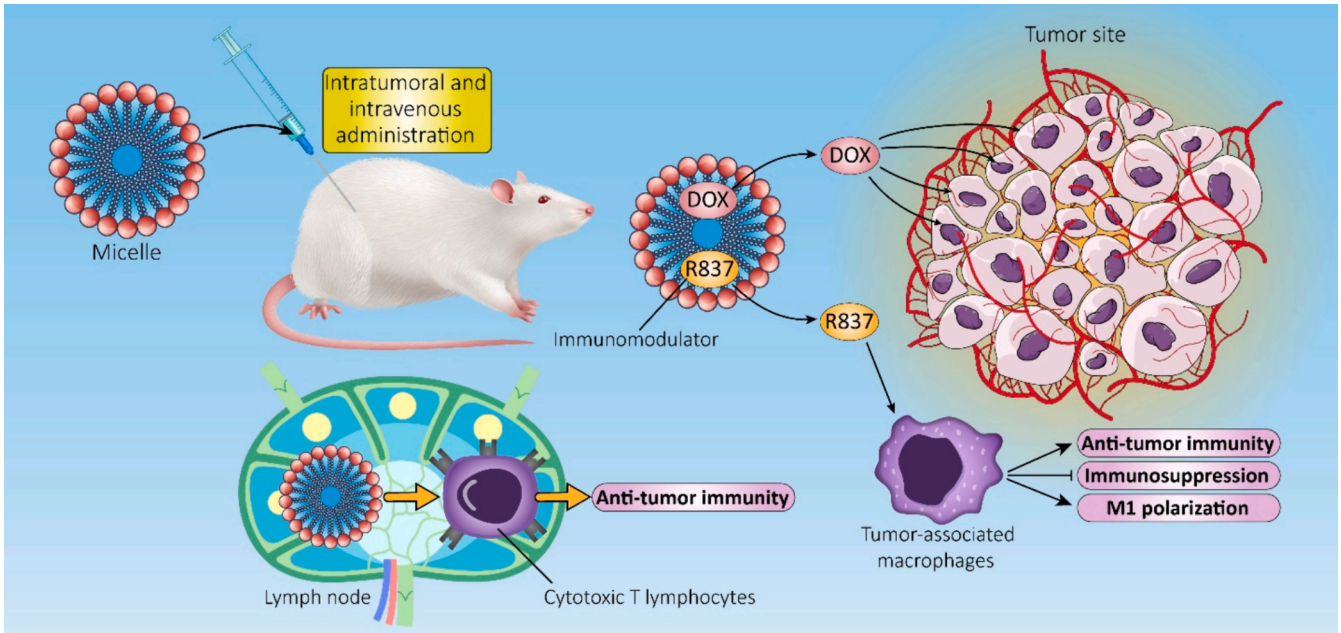

Fig. 9. Micelles in cancer immunotherapy. The targeted accumulation of micelles in lymph nodes and enhancing infiltration of cytotoxic lymphocytes in TME promote anti-tumor immunity can be observed. Furthermore, micellar nanoparticles induce M1 polarization of macrophages to elevate immunity.

responsive to pH. Regarding to physicochemical properties of micelles, which are self-assembled from amphiphilic polymers, this class of materials is capable of loading hydrophobic anticancer drug molecules into its inner core followed by performing a sustained release over time or even burst release due to the change in pH. Another plus for micelle carriers is their stable structure and appropriate size, both of which lead to longer blood circulation time and so better accumulation in the tumor's site because of the enhanced permeation and retention (EPR) effect [174]. In recent years, different types of pH-sensitive micelles have been developed [175–177]. A pH-sensitive copolymer composed of polylactic acid and poly(β-amino ester) was synthesized capable of forming polymeric micelles to load doxorubicin for cancer therapy. Notably, the pH-sensitive agent of this carrier was poly(β-amino ester) with a pK_b of 6.2, above which it is insoluble due to deprotonation, but below this value, it undergoes protonation followed by being soluble in the medium. The doxorubicin-loaded micelles significantly prevented

Table 4
The micellar nanoparticles for the purpose of immunotherapy in cancer.

Nanoparticles	Cargo	Particle size (nm) Zeta potential (mV) Encapsulation efficiency (%)	Cancer type	Remarks	Refs
Polypeptide-based micellar nanoparticles	CH223191 as an AhR inhibitor Anti-CD28	162.6 nm 31.7 mV	Breast cancer	AhR down-regulation leads to reduced immunosuppressive activity and suppresses cancer invasion Exerting synergistic impact between AhR inhibitor and anti-CD28 in cancer immunotherapy	[163]
Polymeric micelles	6-thioguanine	–	Melanoma	Decreasing the number of circulating myeloid-derived suppressor cells Increased anti-tumor immunity in animal model	[164]
HCtSA-OVA micelles	–	86.27 and 105.41 nm 22.95 and 18.57 mV	Melanoma	Surface modification of micelles with dendritic cell membrane to provide a vaccine with accumulation in lymph nodes and boosting anti-tumor immunity	[165]
Polymeric micelles	IDO PD-L1	43 nm	Lung and breast cancers	Accumulation in the tumor site Migration of micelles to lymph nodes Suppressing tumor growth Providing both immunotherapy and photothermal therapy	[166]
Polymeric (PEOz-PLA) mixed micelles	Antigen ovalbumin CL264 (TLR agonist)	54.2 nm −20.7 mV	–	Rapid accumulation at lymph nodes Carboxylated nanoparticles internalized in cells via scavenger receptor-mediated endocytosis Induction of CL264 in endosomes leads to anti-tumor immune response Mediating endosomal escape Boosting MHC I antigen presentation Accelerating antigen release	[167]
Mannose modified stearic acid-grafted chitosan micelles	–	94.16 nm 11.84 mV	Melanoma	Capturing endogenous antigens and promoting antigen uptake by dendritic cells for cancer immunotherapy Mediating anti-tumor responses by CD4 + and CD8 + T cells	[168]
Polymeric micelles	Short peptide antigens	100–200 nm	Melanoma	GSH leads to the cleavage of disulfide bonds to mediate the release of pristine antigens and overexpression of co-stimulatory molecules Stimulation of CD8 + T cells to induce anti-tumor immunity	[169]

the proliferation of HepG2 cells while showing high biocompatibility towards healthy cells [178]. A self-assembled drug delivery system based on poly(β-amino ester) and stearate-modified hyaluronic acid was designed against ovarian cancer. Paclitaxel drug was loaded through the micelle, and the results implied that the drug-loaded carriers were effectively accumulated through the tumors with desirable anticancer activity and also the carrier exhibited high cytotoxicity against SKOV-3 cells [179]. A recent study has also taken advantage of the pH-responsivity of poly(β-amino ester) to come up with a new micelle-like drug delivery system through Michael-type step polymerization. The system consisted of 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)], which has been conjugated to poly (β-amino ester). Through fluorescence spectrophotometry, the critical micelle concentration was found to be 4.5 mg L^{-1} which is potentially suitable for drug delivery applications. Upon the change in the pH, the carriers' size and distribution were altered, and the drug release study revealed the pH-dependent behavior of the micelles [174]. Nonetheless, other pH-responsive groups have been adopted for the development of self-assembled micelles. One of these groups is poly(2-azepane ethyl methacrylate) which was bridged to poly(2-methacryloyloxyethyl phosphorylcholine) to have both prolonged circulation time and pH responsivity in the tumor medium. Regarding the zwitterionic phosphorylcholine groups in the structure of poly(2-methacryloyloxyethyl phosphorylcholine), this polymer is highly resistant to protein adsorption, culminating in an acceptable biostability during the treatment time [180]. Another innovative drug delivery system that has been designed for metastatic breast cancer was based on paclitaxel-loaded polyethylene glycol and poly[(1,4-butanediol)-diacrylate-β-N,N-diisopropylethyl-enediamine]. The drug-loaded micelle was then encapsulated into a $Ly6C^{hi}$ monocyte-based vector. This vector is an immune cell that can actively home to the tumor environment. The micelle exhibited about 10-fold more cytotoxicity to 4 T1 cells than Taxol. It is noteworthy that the targeting ability of the $Ly6C^{hi}$ vector is not related to either the EPR effect or the tumor morphology (Fig. 10) [181].

8.2. Redox responsive micelles

Under some specific pathological conditions like cancer, some moieties, including reduced glutathione (GSH) and ROS are overexpressed through the affected cells. Nanomaterials equipped with redox-sensitive linkages are able to liberate their cargo in the site of action due to the breaks in the linkages. Notably, the concentration of GSH is high throughout the cancerous cells and this content is nearly two-fold compared to the surrounding medium outside of the cell. Moreover, ROS is another factor even reinforcing the secretion of GSH because the cells try to encounter ROS and so produce more GSH (seven-fold) [182]. Therefore, the modification of drug delivery systems with redox-responsive moieties has aroused considerable enthusiasm for targeted cancer therapy.

Based on the conjugation of different types of anticancer drugs with polymeric micelles through disulfide linkages, various redox-responsive micelles have been designed for cancer therapy. It is important to notice that chemotherapy is inhibited by multidrug resistance and hence more effective strategies have been taken. Paclitaxel, along with siRNA, was co-loaded into a micellar system, which was activated through intracellular redox. The main aim of the co-delivery was to target polo-like kinase 1 and increase the therapeutic efficacy for multidrug-resistant cancer therapy. The redox-responsive nature of the delivery system allowed the activation of adenosine triphosphate-depletion action. Moreover, the dual release of paclitaxel and siRNA together culminated in more effective tumor growth inhibition than adopting only one of those agents [158]. A GSH-responsive core-crosslinked micellar system with tunable swelling properties was designed for multidrug resistance cancer therapy. The efficacy of the drug carrier was tested against drug-sensitive and drug-resistance cancer cells. A significant decrease in the IC_{50} of drug-resistant cancer cells was observed after being treated with the doxorubicin-loaded micelles. Moreover, the decrease was even more intensified when verapamil, as a P-glycoprotein inhibitor, had been loaded with doxorubicin into the micelles [183]. As it was mentioned, the high level of GSH is accompanied by an excessive amount of ROS in the tumor microenvironment, but most of the studies have designed

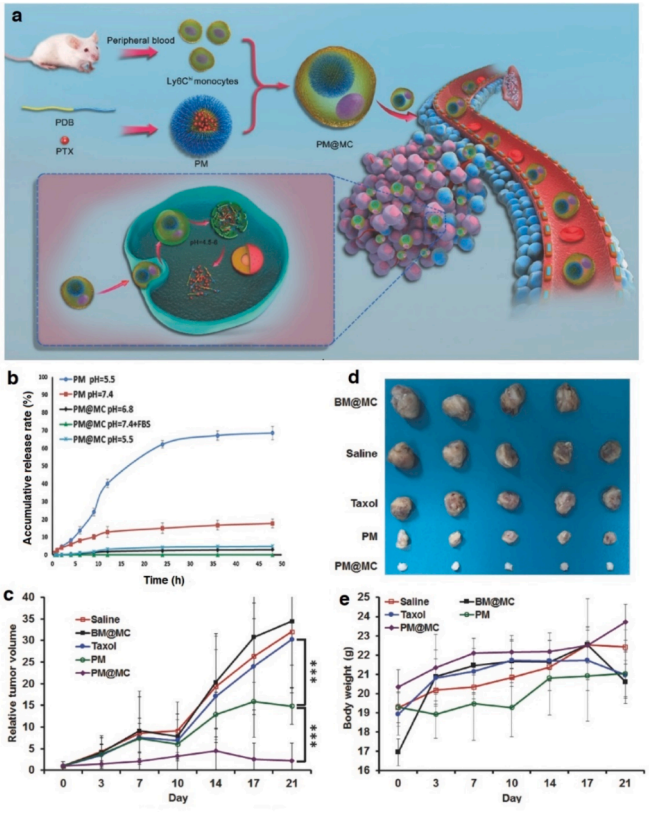

Fig. 10. Tumor targeting through using the drug-loaded micelle encapsulated into Ly6C^{hi} monocytes. (a) A scheme on the self-assembly of the pH-sensitive micelles and PTX loading followed by being entrapped into Ly6C^{hi} monocytes. The carrier was endocytosed through the tumor cell, and the loaded monocytes fused with lysosomes and dissociated under the acidic condition inside, releasing the cargo. (b) The accumulation release rate (%) of PTX from various samples through different pHs. (c) The relative tumor volume after being treated with different samples. (d) The excised tumors at the end of the experiment were treated with different samples. (e) The change in the body weight during the experiment. ***$p < 0.001$. Abbreviations: paclitaxel (PTX), PTX-loaded micelle (PM), the PM-loaded monocyte (PM@MC), the blank micelle-loading monocyte (BM@MC). Reprinted from [181] with permission from Wiley.

micellar systems responsive to either GSH or ROS, and the need for a more effective system responsive to both stimuli can be felt [184,185]. A recent study has reported the synthesis and anticancer potential of a dual-responsive micellar delivery system. Gemcitabine, as an anticancer drug, was loaded into the micelle through a disulfide bond. The drug release through physiological conditions was very low (3.33 %), while in the exposure of GSH and ROS (0.1 % H_2O_2), the drug release reached up to 90 % after 48 h. The in vitro and in vivo studies revealed the efficacy of the dual-responsive micellar delivery system with the antitumor ability and minimum side effects [162].

8.3. Light-responsive micelles

Adopting light as an external stimulus gives an opportunity to remotely activate light-responsive agents and take control over the release of entrapped drug molecules, resulting in improved therapeutic efficacy while avoiding drug leakage in off-target tissues or organs. Generally, ultraviolet (UV) and near-infrared (NIR) are two widely applied light sources for biomedical applications; the former has weak penetration and leaves undesirable effects on healthy tissues [186], whereas the latter is extensively applied rooting in its merits like higher penetration with minimal side-effects, simple operation, and good controllability [187].

Triggered by UV, a study has come up with an ultrasensitive UV-responsive micellar drug delivery system. To minimize the negative effects of UV, short-term irradiation (10 s) was applied, which resulted in a rapid and complete release of entrapped doxorubicin from the micelles due to the disruption of UV-sensitive linkers (maleimide-anthracene) [188]. Apart from the role of light on the drug release rate, NIR irradiation can be employed for photothermal (PTT) and photodynamic therapies (PDT). PTT relates to the adoption of an agent that is capable of converting light to heat, followed by an increase in the local temperature where it had been incorporated [189]. This type of treatment is of particular interest mainly because it can be used for each type of cancer without being worried about having multidrug resistance. It is worth mentioning that PTT is in clinical trials with very promising results, including the ablation of 94 % of prostate tumors of patients undergoing this type of treatment [190]. On the downside, this therapy approach has some challenges that should be addressed, including the low heat conversion efficiency, weak accumulation of PTT conventional agents throughout the tumor, recurrence of the tumor after PTT monotherapy, etc. [191]. As one of the prominent advantages of micelles is their accumulation throughout the tumor's structure via the EPR effect, their combination with PTT and PDT agents can be an effective strategy in cancer therapy.

A light-responsive multifunctional micellar system was designed based on indocyanine green, gambogic acid, poly(ethylene glycol), and thioketal. The micelle showed excellent tumor accumulation and great NIR conversion; applying 808 nm irradiation was synchronized with the formation of ROS and an increase in the tumor's temperature. Moreover, the irradiation caused the release of gambogic acid into the tumor's cells. The combination of chemo- and PTT therapy resulted in an excellent tumor inhibition rate (97.9 %) of breast cancer models (4 T1 in a mouse model) (Fig. 11) [189].

Another type is PDT, which is the same as PTT, but it produces ROS locally as the result of light irradiation, and the excessive ROS causes the cancer cells' viability to decrease significantly [192]. Nearly one century has passed since the discovery of this therapeutic approach with numerous benefits such as insignificant invasiveness, high selectivity in the tissue of tumor, and low cytotoxicity [193]. In this approach, there is a photosensitizer, and after being irradiated with a specific wavelength of light, its ground state will be excited and form a short-lived singlet state followed by being turned into a long-lived triplet state. Through the interaction of intracellular molecules with the photosensitizer (triplet state), the ROS, including hydrogen peroxide, etc., will be generated, and these products are highly toxic to cancer cells [194]. There are some problems revolving around PDT therapy through micelles, one of which is insufficient release of photosensitizers from the micelles, and another one is related to the hypoxic region of the tumor microenvironment [129,195]. It is critical to bear in mind that the efficacy of PDT therapy is highly dependent on the oxygen concentration, and due to the existence of hypoxic regions, specifically in the sites distanced from the blood vessels, PDT cannot reveal its therapeutic effects in these regions [196]. To address the insufficient release of photosensitizer agents, a dual-step irradiation strategy was applied. Chlorin e6, as the photosensitizer, was loaded into the micelles composed of methoxypolyethylene glycol and thioketal. After the co-incubation of micelles with cancer cells, a short-time irradiation was applied to stimulate the liberation of chlorin e6, and the next irradiation was applied 2 h later for a longer time. This two-step strategy drastically enhanced the generation of singlet oxygen culminating in more effective cancer therapy [195]. A new platform has been designed against hypoxic tumors. The ruthenium-containing micelles contained red-light-cleavable moieties, and the drug release was oxygen-dependent. The results revealed that the micelles could successfully reach the hypoxic regions with efficient tumor growth inhibition [129]. Another challenge of NIR-activated nanomaterials is the need for prolonged NIR irradiation, which is accompanied by undesirable effects on healthy tissues. A

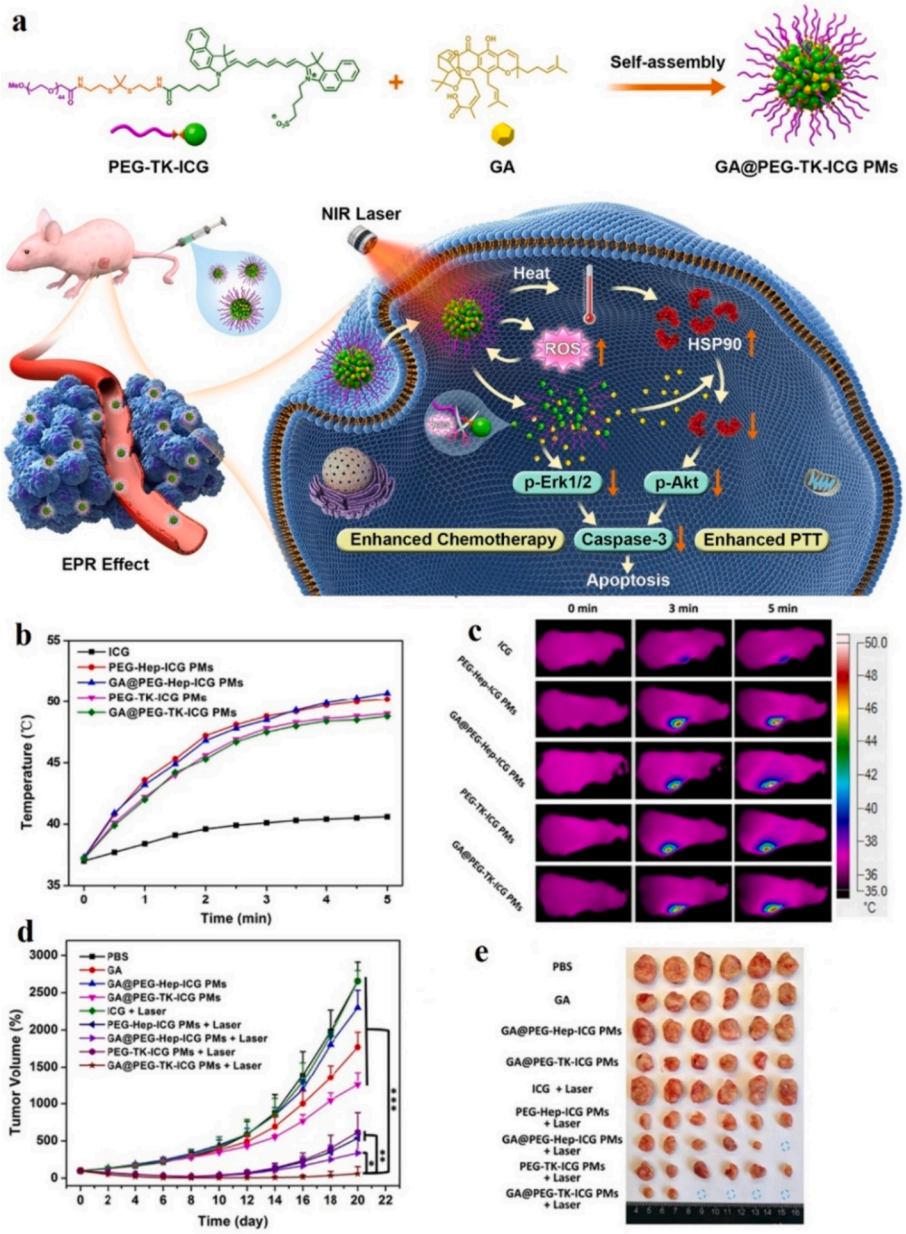

Fig. 11. A multifunctional micellar system with synergistic chemo- and PTT therapies for aggressive breast cancers. (a) A schematic of the production and potential application of GA@PEG-TK-ICG PMs towards breast cancers. (b) Assessment of intratumoral temperature and (c) in vivo thermal images of tumor-bearing (4 T1) mice after being exposed to 808 nm NIR irradiation with different samples. (d) The tumor volume after being treated with different samples with and without laser irradiation. *, **, and *** stand for $P < 0.05$, $P < 0.01$, and $P < 0.001$, in turn. (e) The photographs related to the excised tumors after 20 days of treatment with different samples. Abbreviation: gambogic acid (GA), poly (ethylene glycol) (PEG), thioketal (TK), indocyanine green (ICG), polymeric micelles (PMs), and heptyl (Hep). Reprinted from [189] with permission from Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

fast-ignited micellar system has recently been developed for the rapid release of loaded drugs once the irradiation has applied. The erbium-doped micelles exhibited a hydrophilicity conversion just after 5 min NIR irradiation which led to a complete disruption of micelles followed by a fast release of doxorubicin. Moreover, the irradiated NIR caused the production of NO by which the P-glycoprotein-mediated doxorubicin efflux was diminished (Fig. 12) [197].

8.4. Multi-responsive micelles

Recapitulating more than one stimulus-responsive agent in a platform has the potential to increase the efficacy, accuracy, and flexibility of cancer therapy. The multi-responsive materials may consist of some linkages and/or materials responsive to both internal/external stimuli [189]. In response to dual or multiple stimuli, different delivery systems have been designed and synthesized, and these combinatory triggers are as follows: endosomal and lysosomal pH, pH/GSH, pH/redox, and metalloprotease/pH, etc. [176,198]. One step further is to add some exogenous stimuli, such as magnetism, light, ultrasound, etc., to those endogenous ones to increase the precision of drug release at the tumor's site. Apart from drug release into the tumor's microenvironment, these external-based stimuli-responsive agents can play their role, like increasing the local temperature in response to an external magnetic field, ultrasound, and light (NIR, UV, etc.). In the case of ultrasound-responsive nanomaterials, they can affect cancerous cells through different mechanisms when exposed to ultrasound waves, including

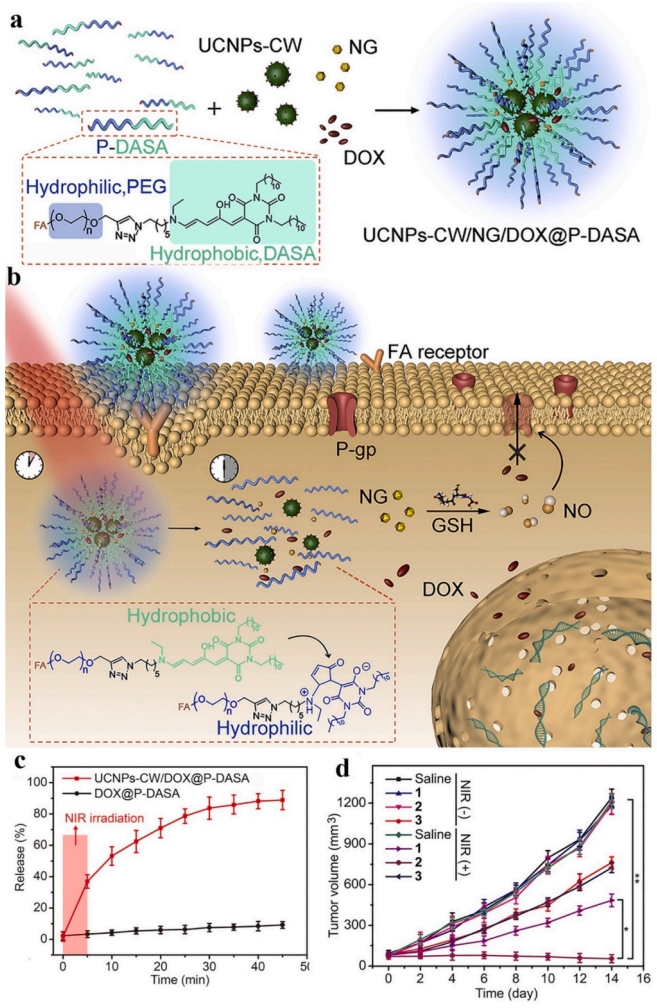

Fig. 12. A fast drug release from self-assembled micelle after NIR irradiation for efficient cancer therapy. (a) The process of self-assembly of the micellar delivery system, and (b) the rapid disruption of micelles once the NIR has been applied, followed by the liberation of entrapped drug molecules and NO generation. (c) The drug is released from different samples with and without NIR. (f) The changes in the tumor volume of mice up to 14 days of treatment with saline, UCNPs-CW/DOX@P-DASA (1), UCNPs-CW/NG/DOX@P-DASA (2), and doxorubicin (3) with and without NIR irradiation for 5 min. Abbreviations: doxorubicin (DOX), upconversion nanoparticles (UCNPs), UCNPs modified with IRDye®800CW (UCNPs-CW), donor–acceptor Stenhouse adduct (DASA), and nitroglycerin (NG). Reprinted from [197] with permission from Elsevier.

cavitation and temperature increase. Nonetheless, the magnetic- and light-responsive materials are capable of raising the cells' temperature to a level at which cell death occurs [199]. It is worth mentioning that the type of cell, the temperature, and the time of applying heat are the main governing factors when it comes to hyperthermia-based therapies. When the local heat rises up to 43°*C*, different compartments of cells, such as membrane fluidity, undergo a change in their function. Maintaining the temperature would be synchronized with an alteration in the cell's shape and cytoskeleton, and the cell morphology changes to round- and flattened-like morphology depending on the type of cell [200].

A dual-sensitive micellar delivery system responsive to pH and redox has been synthesized through an amine epoxy ''click'' reaction at room temperature. The existence of disulfide linkages in the inner structure of micelles provides a compact core–shell architecture in normal situations while rapidly liberating the entrapped drug molecules once exposed to reductive agents. The tertiary amine groups are responsible for releasing the cargo at mildly acidic conditions of the tumor environment [201]. A schematic of the responsivity of the proposed delivery system shows how demicellization occurs in the exposure of pH, redox, and pH/redox. As the combination of external and internal stimuli has been reported to have more efficacy, hencemore attention has been devoted to micelles responsive to both of them [176]. A pH- and NIR-responsive micelle-based delivery system was reported for multidrug-resistance breast cancer therapy. At physiological conditions, the micelles showed a particle size of 30 nm, while in a mildly acidic medium, the micelles dissociated and liberated the drug molecules. Moreover, after NIR irradiation, the tumor penetration of micelles was significantly enhanced and the drug's release was found to be tuned with the hyperthermia effect. The combination of pH- and NIR-responsivity led to an inhibition in the growth of MCF-7/ADR breast cancer in vivo [202]. A triple-stimuli (pH, redox, and light) nanocarrier was designed for precise cancer therapy. A smart drug release was observed when the nanocarrier was exposed to the pH and reduction stimuli, and the release rate was boosted when the NIR irradiation was applied. The in vivo results implied that the multi-responsive micelles exhibited improved cellular uptake and tumor accumulation, and the hyperthermia caused a fast phase transition followed by a tumor ablation because of the synergistic effect of thermo- and chemotherapy [176].

9. Bioimaging and theranostic approaches

The importance of imaging in cancer diagnosis and therapy is clear to the community. The nanomaterials equipped with imaging agents are capable of getting valuable information about the targeted tissue on the one side and tracking the treatment efficacy on the other side. The micelles' clinical applications as the matrix for imaging agents' delivery are based on the unique features of these self-assembled materials. After the administration of contrast agents-loaded micelles, the imaging agents are supposed to delineate the targeted tissue/organ on the images. The most reputable and widely used diagnostic agents are radioactive metals, magnetic metals, and organic iodine for scintigraphy, MRI, and CT, respectively. It has been revealed that micellar systems are able to carry all the diagnostic agents with great clinical outcomes. There are some requirements when it comes to the design of micelles for contrast agent's delivery. The micellar shell should protect the agent from the reticuloendothelial system, thus preventing rapid clearance from the blood circulation, and as the particle size has a pivotal role in the destiny of the carrier, it must be taken into consideration.

As a medical imaging technique, MRI is being widely applied in medicine for diagnosis and follow-up of a disease using strong magnetic fields to form images related to the body organs [203]. Various MRI agents have been incorporated into the different types of micelles for imaging purposes among which Gd-chelates are of particular interest. A peptide amphiphile micelle modified with Gd chelator diethylene-triaminepentaacetic acid (DTPA) was developed for MRI imaging. The micelles morphology was found spherical and cylindrical and the histology studies revealed that no necrosis took place. All the micelles were cleared through the reticuloendothelial system and renal clearance, as the complete removal of Gd-chelates may be problematic [204]. Gd-DTPA as a T_1-weighted MRI agent, along with an anticancer cancer, was encapsulated through a polymeric micelle system for simultaneous diagnosis and therapy. The tumor contrast enhancement occurred when the administration of micellar carriers through the hepatic artery had been performed [205]. A diagnostic platform consisting of ^{89}Zr-, and Fe^{3+}-labeled polymeric micelle has been fabricated for MRI and positron emission tomography. This study has made a comparison between the labeled micelles and Gd-based contrast agents [206]. It is known that because of rapid renal clearance of Gd-based agents, they are considered safe. However, their combination with micelles raises concern as there would be a risk for cytotoxicity. Generally, the particles with a size of 5 to 6 nm are excreted through renal, and the Gd-chelates micelles size is beyond that. Hence the liver and spleen would take them up, followed

by an increase in Gd in the tissues; the accumulation of Gd-based agents can induce long-term cytotoxicity [207,208]. Similar to conventional Gd-chelates, the Fe-labeled micelles had T_1-contrast and did not induce nephrogenic systemic fibrosis, restricting the clinical applications of Gd-based agents. Through anticipation made in this study, it was mentioned that the Fe-labeled micelle was safe as deferoxamine is clinically approved, and the amount of Fe was less than the cytotoxicity threshold. The imaging potential of ^{89}Zr-Fe^{3+}-labeled polymeric micelle was also assessed, and the tumor lesions were detected through the body via positron emission tomography, and besides yielding high-resolution images through MRI, this technique revealed the intratumoral distribution of nanoparticles [206]. An anticancer drug-loaded triblock polymeric micelle comprised of hydroxamic acid chelating iron throughout the structure was formed as a theranostic platform. The integrity of micelles was drastically improved as the result of iron incorporation and also the circulation pharmacokinetics of loaded drug was extended compared to the free drug. Speaking of MRI imaging, the paramagnetic properties of iron culminated in contrast in the tumors;

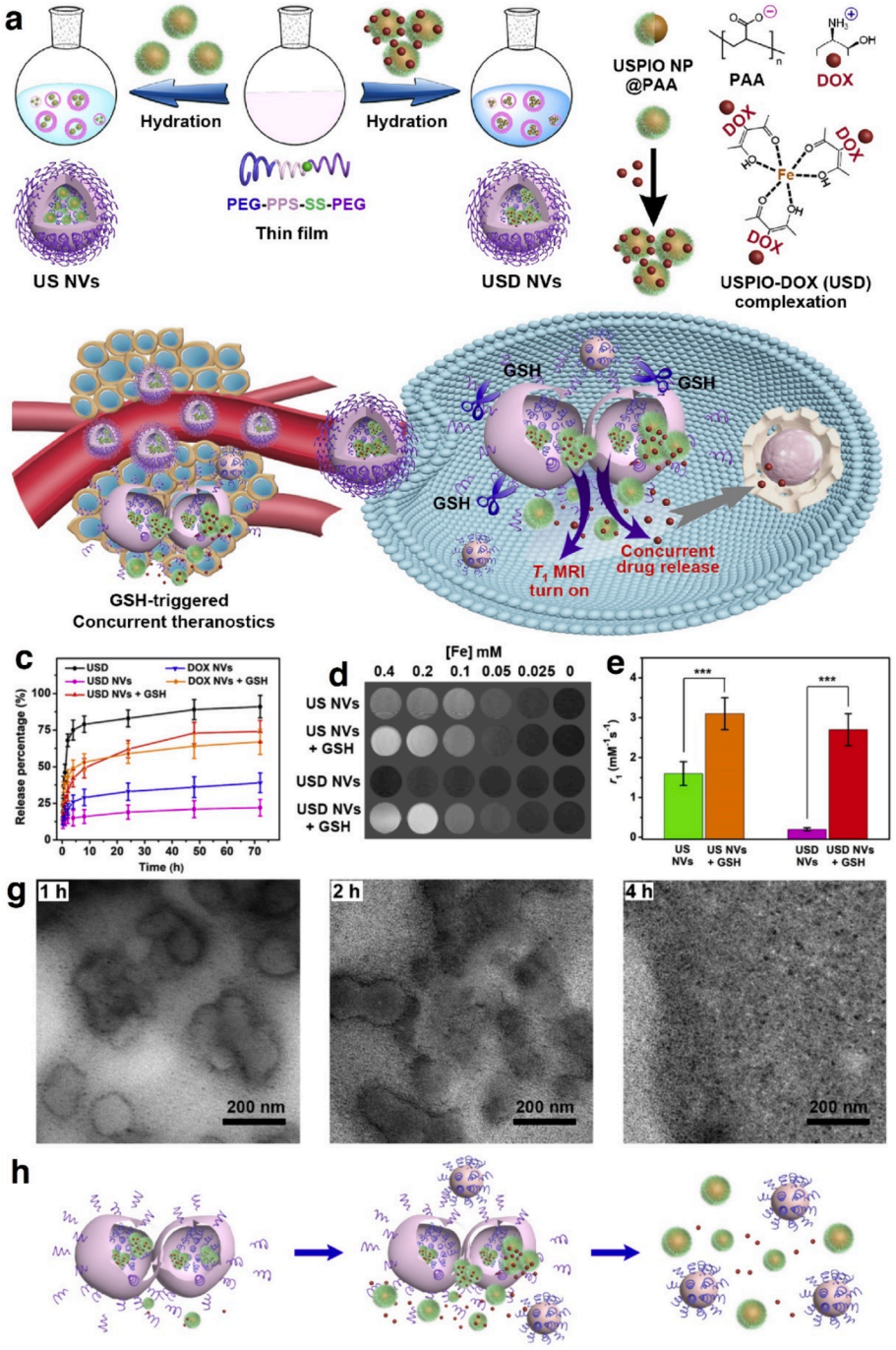

Fig. 13. A smart micellar platform for concurrent cancer therapy and imaging. (a) An illustration of micelles preparation along with (b) its drug and iron oxide nanoparticles release in the exposure of GSH. (c) The drug release behavior from different samples with and without being exposed to GSH. (d and e) MRI phantom and r_1 values related to each sample with and without exposure to GSH. ***$p < 0.001$. (g and h) The TEM micrographs and the scheme related to each micrograph show how GSH causes the dissociation of micelles and the release of anticancer drug molecules and the MRI agents. Abbreviations: Poly(acrylic acid) (PAA), PAA-coated ultrasmall paramagnetic iron oxide nanoparticles (USPIO NPs), doxorubicin (DOX), nanovesicles (NVs), and poly(ethylene glycol)-poly(propylene sulfide)-SS-poly(ethylene glycol) (PEG-PPS-SS-PEG). Reprinted from [210] with permission from Elsevier.

the iron-stabilized micelles accumulated through the tumor tissue, and that was the reason why a sufficient contrast in MR imaging was provided. The biomarker imaging can also be obtained through positive magnetic resonance contrast of the iron-stabilized micelles for clinical applications [209]. Tracking the treatment efficacy is of great importance as step by step, the inhibition of tumor growth can be observed if the treatment is effective [173]. A smart GSH-responsive theranostic micellar system encapsulating doxorubicin as an anticancer drug and superparamagnetic iron oxide nanoparticles as the MRI contrast agent was synthesized for synergistic cancer therapy and imaging. The platform gives an opportunity to release the cargo and the iron oxide nanoparticles (T_1 contrast agents) once it has been exposed to GSH in the tumor microenvironment, culminating in the eradication of the cancerous cells and tracking the treatment procedure (Fig. 13) [210].

As a non-invasive technique, fluorescence imaging is another technique by which the visualization of biological processes, tissues, and organs can be performed. At a certain wavelength, the luminescence agent absorbs light or electromagnetic radiation resulting in the emitting light [211]. To increase the benefits of this technique in bioimaging, the agent or probe must be hydrophilic with desirable solubility in water, photostable, and biocompatible. This is the case particularly in the wavelengths above 500 nm, a photostable probe would decrease the auto-fluorescence emitted through bio-tissues [211]. A pH-responsive 'on-off' folate-modified polymer micelle with theranostic potential was designed. To endow the delivery system with fluorescence imaging, quantum dots were incorporated and a comparison has been made between the non-targeted and targeted accumulation in the tumor tissue. By only adopting fluorescence imaging, the tracking of nanoparticles was possible [212]. Somewhere else a nanomicelle as a bio-probe was reported for image-guided cancer therapy. It was composed of perylene diimide as the fluorescence agent and block copolymer poly(D,L-lactide)-b-poly(ethyl ethylene phosphate). The distribution of nanomicelles was tracked through ex/in vivo fluorescence imaging. After intravenous injection of nanomicelles, in vivo fluorescence images from the treated mice were taken up to 4 h, and it is visible that the tissue penetration depth of nanomicelles was limited [213]. On the downside, this may be the main disadvantage of this technique. Another challenge regarding conventional molecular probes for cancer diagnosis is their 'always-on' feature restricting their abilities in diagnosis as different cancer types have complex environments and a variety of targeting efficiencies. A color-convertible responsive hydrogen peroxide (H_2O_2) was synthesized to address this challenge. The micelle bio-probe was designed as a way to delineate tumor tissue from the normal ones through fluorescence imaging. The distinguished advantage of this system over the rest is its color-convertible nature; in the exposure of H_2O_2, the micelles undergo a change in the fluorescence color from blue to green, and as H_2O_2 is significantly higher in tumors than the normal tissue, we can only see the images in green when it represents the tumor [214]. This strategy increases the accuracy of diagnosis and holds a promising potential in theranostic applications (Fig. 14).

10. Hybrid nanoparticles

Polymeric micelles with an amphiphilic nature are known as self-assembled nanomaterials capable of encapsulating hydrophobic moieties in their inner core while having a hydrophilic shell on the outer layer when dispersed in an aqueous medium. As these carriers can improve the stability of encapsulated cargo followed by providing a sustained/targeted release, considerable attention has been given to them for biomedical applications [215]. It is worth mentioning that to

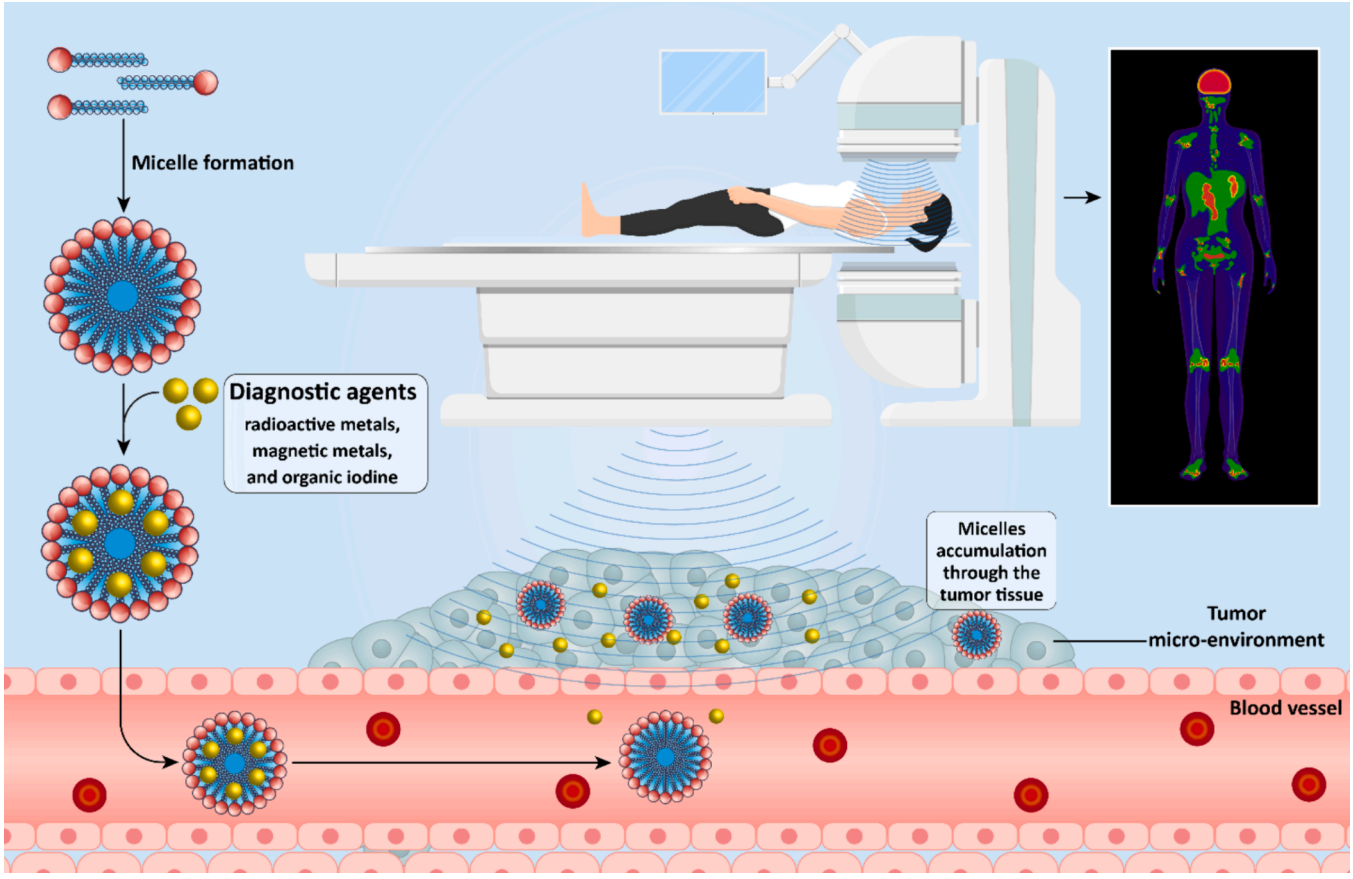

Fig. 14. Micelles for the purpose of bioimaging. As micelles demonstrate a high accumulation rate in the tumor site, they can be considered promising agents for the purpose of imaging. Furthermore, there are a number of biomarkers associated with each type of cancer that can be used for diagnosis of cancers.

endow these micellar systems with stealth behavior, poly(ethylene glycol) (PEG) as the first strategy is in the micelles' structure and observable in most studies, among which PEG-poly(lactic acid), PEG-poly(lactic-co-glycolic acid), and PEG-poly(ε-caprolactone) can be enumerated [216–218]. Although some of them, such as PEG-block-poly (aspartic acid) loaded with doxorubicin, are in the clinical trial (phase two), there are still challenges on the downside [219]. The major obstacle to those micellar delivery systems is the reticuloendothelial system; despite the fact that PEG provides a long circulation through the bloodstream, the content of micelles entering the tumor microenvironment is still limited. Speaking of numbers, nearly 95 % of administered micelles fail to reach the tumor and find themselves in the liver and spleen, and only the rest (5 %) accumulate in the tumor thanks to the EPR effect [220]. Another limitation relates to the non-degradability of PEG, which causes limited drug release [221].

In order to reinforce the antitumor efficacy of micelles, turning micelles with singular-functionality towards multi-functionality is needed, and this pluro-functionality is dependent on the type of used polymers and/or some other extra agents [215,222]. It is noteworthy that single micellar systems' potential for antitumor activity is limited, and in order to overcome these restrictions, developing a new class of micellar systems called hybrid is inevitable [215]. Hybrid micelles relate to those systems composed of either two different block co-polymers or a single polymer combined with an extra agent, such as inorganic nanomaterials. The hybridization culminates in a micellar structure with improved stability and multifunctionality thanks to each component involved. Moreover, even if it is possible to develop a multifunctional micellar system with a single polymer, the synthesis procedure can be complicated and time-consuming, but hybrid micelles provide an easier approach to recapitulate the desirable properties into one package [223]. In this section, the hybrid micelles role in cancer therapy is covered; these systems have been formed from either two different polymers or combined with other agents.

As mentioned before, the PEGylation alone is not good enough to concurrently prolong the micelle's circulation time and accumulation in the tumor's structure. Moreover, the weak degradation rate of PEG was another obstacle to the PEGylated micelles' anti-tumor efficacy. To address those problems, a hybrid micellar system composed of PEG-poly (L-lactic acid) (PEG-PLLA) and poly(aminoethyl ethylene phosphate) (PAEEP)-PLLA was designed for anticancer purposes. In contrast to PEGylated micelles, the hybrid one resulted in a prolonged circulation time and the accumulation of micelles in the liver and spleen was decreased. Speaking of anti-tumor activity, the penetration of hybrid nanoparticles into the tumors increased, followed by faster drug release inside because of a higher degradation rate of PAEEP in endo- and lysosome than PEGylated micelles. In this study, a comparison has been made between the tumor growth inhibition of PEG-PLLA and the hybrid and it turned out that the latter had 84.5 % while the former inhibited the tumor growth by about 44.5 % [215]. A theranostic hybrid micellar platform consisting of two diblock co-polymers—polyethylenimine-polycaprolactone and Gd-DTPA-PEG-polycaprolactone was developed. The hybrid nature of micelles led to escape from endo- and lysosome, followed by liberating the entrapped drug molecules in the nucleus. Besides doxorubicin, microRNA-34a was encapsulated in the inner side of the hybrid micelle, and its release downregulated cyclin D1, CDK6, Bcl-2, and Bax expression on the one hand and inhibited the breast cancer cells' migration and proliferation on the other hand. Nonetheless, the Gd-chelates, which were conjugated to the hybrid micelles, improved MRI contrast to solid tumors [224]. Somewhere else, an upconvertable compound was combined with a photosensitizer agent (Ce6) for chemo-photodynamic therapy. The micelle was designed to be ROS-responsive and composed of PEG-b-poly-(propylene sulfide); the micelles were co-assembled with NaErF4:Tm@NaYF4 to yield the hybrid system. At very low power laser density, excessive ROS was generated, leading to the fast release of entrapped drug molecules in the cancer cells. Moreover, in the exposure of 980 nm irradiation, significant antitumor activity was obtained thanks to the synergistic effects of chemo- and photodynamic therapy [225].

Multifunctional hybrid micelles composed of a mono-, di-, and/or triblock copolymer plus one or more inorganic compounds are of particular interest in cancer imaging and therapy. The role of inorganic compositions in the hybrid structure is to induce imaging, hyperthermia, endowing the carrier targetability, etc. Calcium phosphate is one of those inorganic compounds incorporated in the various micellar platforms, rooted in the antitumor activities it has shown [226]. Moreover, calcium phosphate-based nanomaterials have been found to improve biocompatibility and biodegradability, and they have desirable permeability [227,228]. A hybrid micellar system comprised of PEG, poly (glycerol sebacate), and hydroxyapatite as the most reputable member of the calcium phosphate family, was applied for cancer therapy. The hydroxyapatite in the structure was found to interact with carboxylic acid groups of PEGylated poly(glycerol sebacate) through calcium ions. The interaction resulted in three advantages for the hybrid system—appropriate chemical stability, targetability, and sustained release ability. Through optimizing the synthesis parameters—the concentrations of hydroxyapatite and PEGylated poly(glycerol sebacate)—homogenous hybrid nanoparticles in the range of 20–30 nm were successfully synthesized. The in vivo results implied that the hybrid system loaded with doxorubicin showed a high antitumor efficacy while leaving no adverse effects [165]. Calcium phosphate-based micelles combined with PEG, polyanion block co-polymers, and Gd-DTPA were used for theranostic applications. A dramatic accumulation of nanoparticles in the tumor's microenvironment was observed which is beneficial to MRI through making a distinguishable contrast [223].

Hyperthermia is one of the well-known therapeutic approaches in anticancer treatments. Regarding the applied temperature, a desirable range was reported from 41 to 46°C. Below the minimum value, there would not be any effect on the cancerous cells (low efficacy) and above the maximum value, is beyond the tolerance of healthy cells, undergoing necrosis. The mentioned range can be considered safe as the eradication of cancer cells takes place while the healthy cells are left intact. Hyperthermia-based therapies can be performed through techniques, one of which is by adopting magnetic agents that are responsive to an external magnetic field, and the other one is through using a light-responsive material capable of turning light into heat. A magnetic polymeric micellar system was formed by embedding superparamagnetic iron oxide in the inner side of self-assembled poly(styrene27-b-acrylic acid120) P(S27-b-AA120). The platform was found to be promising in magnetic-responsive hyperthermia-based therapies [229]. The synergistic effect of chemo- and phototherapy was adopted through a multifunctional light-responsive micelle formulation. Upon being exposed to NIR irradiation, not only did the micelles generate ROS, but they also converted the light into heat, resulting in an increase in the local heat. The combination of photodynamic and photothermal therapies with chemotherapy could be an effective approach towards multidrug-resistant tumors (Fig. 15) [222].

11. Conclusion and remarks

The increasing evidence reveals that cancer treatment requires an interdisciplinary approach, otherwise it will be difficult to find an efficient treatment. The present review revealed that micelles are efficient nanocarriers in the treatment of various cancers and this has been confirmed by various experiments. Various gene therapy approaches using RNAi (siRNA and shRNA) and non-coding RNAs are used in cancer suppression. However, their efficiency could be improved by the employment of micelles to increase their internalization in tumor cells and suppress cancer progression. There is no study about the delivery of the CRISPR/Cas system by micelles that can be the focus of future experiments. In addition, synthetic and natural compounds such as doxorubicin, paclitaxel, docetaxel, curcumin, and quercetin can be delivered by micelles in cancer therapy. Micelles improve the

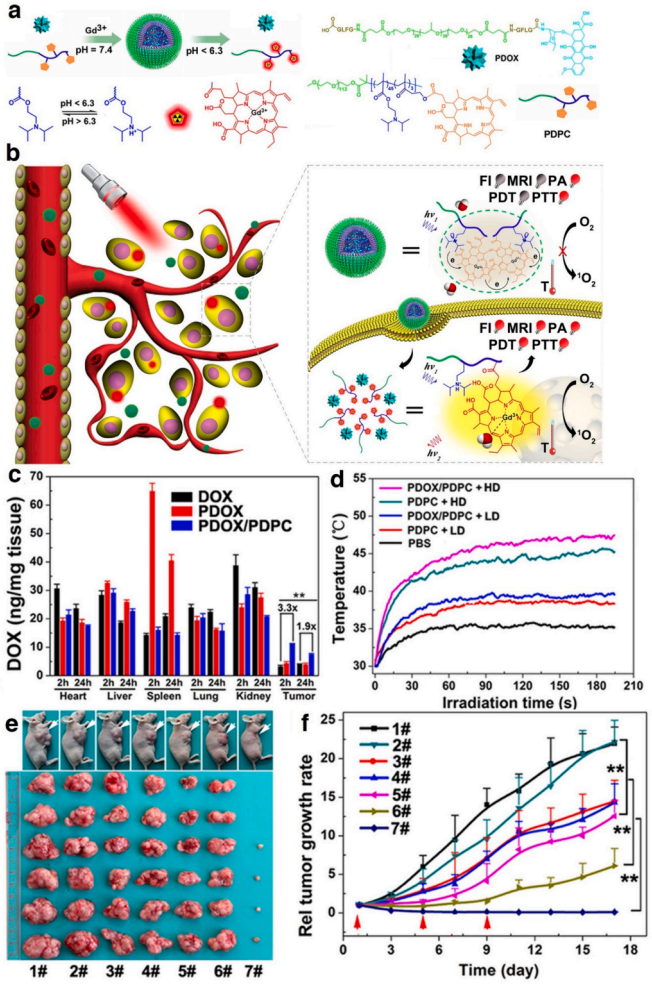

Fig. 15. A multifunctional light-responsive hybrid micellar system for synergistic chemo- and phototherapy. (a) The procedure by which the ternary micelle composed of a pH-responsive diblock co-polymer, Gd-coordinated the photosensitizer agent (Ce6) and doxorubicin was prepared. (b) A schematic of the multifunctionality of robust micelles against multidrug-resistant tumors. (c) The distribution of doxorubicin in the various organs of tumor-bearing mice. (d) Light-converting potential of different samples to heat in vivo (Ce6 dose = 2.5 mg/kg (LD) and 5 mg/kg (HD). (e) The photographs relating to the tumor-bearing mice and the excised tumors at the end of the study; the white arrows show the tumors. (f) The tumor growth inhibition curves related to different samples; the red arrows show the time intervals at which the micelles had been injected. It is noteworthy that when the tumors reached 2000 mm^3, the mice were sacrificed. The samples codes: 1 to 7 in turn attribute to PBS, PDPC, DOX, PDOX, PDOX/PDPC, PDPC + Laser, and PDOX/PDPC + Laser. Abbreviations: poly(ethylene glycol)-block-poly(diisopropanol amino ethyl methacrylate cohydroxyl methacrylate) (PDPA), Ce6-conjugated PDPA micelles (PDPC), doxorubicin (DOX), and the pluronic prodrug of doxorubicin (PDOX). Reprinted from [222] with permission from ACS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

bioavailability of drugs and promote their therapeutic index. Nanoplatforms provided by micelles mediate the co-delivery of drugs and genes in synergistic cancer suppression. The TME remodeling can be affected by micellar nanoparticles which regulate the infiltration of immune cells and modulate their interaction with tumor cells. Besides, micelles can enhance anti-tumor immunity by promoting the infiltration of T cells. Although micelles are promising candidates in cancer therapy, their selectivity towards tumor cells can be improved using surface modification. The modification of micelles with aptamers, hyaluronic acid, and peptide leads to increased internalization of micelles in cancer cells, mainly via receptor-mediated endocytosis.

Conventional micellar drug delivery systems are categorized in the passive targeting group, which means no control is possible once the injection has done. Their anticancer potential depends mainly on the physicochemical properties of the micelle, including particle size, surface groups, etc. The research trend has steered spontaneously to smart and more functional systems as those traditional ones did not seem to overcome the main challenges in the field. Stimuli-responsive micellar systems as smart delivery carriers deserve to substitute the conventional ones because they are able to undergo a change in the size, surface charge, etc., and exhibit enhanced tumor targeting, effective permeability, localized drug release, etc., upon being exposed to various stimuli. There has been considerable attention devoted to single-stimulus micelles, while multidrug-resistant tumors and targeting hypoxia regions of tumors are huge hurdles in cancer therapy requiring more potent approaches. Multistimuli-responsive micelles can be a promising alternative to both the conventional and single-stimulus systems; recapitulating external and internal stimuli agents into one system gives an opportunity to yield a system with more potency. Besides active targeting, imaging is another feature that is being increasingly used in the micelles. The existence of an imaging agent has the potential to delineate the image of the targeted organ and track the therapy in each step. The combination of imaging and therapeutic features gives birth to theranostic micelles. Therefore, equipping a micellar carrier with imaging ability is an added value to take into account. It is critical to bear in mind that micellar delivery systems are generally considered appropriate for cancer therapy as some of them are already being used clinically. Based on the research trendline, it is anticipated that the multifunctional micelles gradually find their way through clinical trials. However, taking complete control over all the stimuli agents simultaneously is still limited and requires more time to become fully practical.

It was previously mentioned that micelles are able to mediate EPR in human cancers because of leaky vasculature, allowing the nanostructures to accumulate at the tumor site due to the size and surface characteristics. The EPR effect is promising in the field of cancer therapy due to the increasing specificity of the nanostructure-based therapeutics and reducing systemic toxicity. Pre-clinical studies have highlighted that an increase in the accumulation of nanoparticles in the tumor site due to the EPR effect can improve therapeutic outcomes in animal models. However, there are some challenges in the clinical studies. The tumor vasculature heterogeneity among patients and the presence of physiological barriers, including interstitial fluid pressure, can decrease the accumulation of the nanostructures at the tumor site. Therefore, the issues in the clinical studies should be considered to design more appropriate micelles for the EPR effect and enhancement in tumor accumulation.

As a final direction, the application of biomimetic nanoparticles in the treatment of human cancers has shown an ascending trend in recent years. For the micelles, a number of studies have applied biomimetic micelles in cancer therapy and drug delivery approaches [230–232]. However, many of the aspects have been ignored, including biomimetic micelles responding to redox, the engineering of cell membranes for responding to enzymes in the TME, using various kinds of membranes obtained from tumor cells, macrophages, cancer-associated fibroblasts, and red platelet cells and comparing their efficacy in cancer therapy, the exact mechanism of internalization in tumor cells, changes in the size and zeta potential as well as encapsulation efficacy that can be comprehensively evaluated in the upcoming studies.

Funding

None.

CRediT authorship contribution statement

Wei Gao: Writing – original draft. **Ashkan Bigham:** Writing – original draft. **Matineh Ghomi:** Writing – original draft. **Ali Zarrabi:** Visualization, Validation, Software. **Navid Rabiee:** Visualization, Validation, Supervision. **Mohammad Reza Saeb:** Visualization, Validation, Writing – review & editing. **Yavuz Nuri Ertas:** Writing – review & editing. **Arul Goel:** Visualization, Validation, Supervision, Software. **Esmaeel Sharifi:** Visualization, Validation, Supervision, Software. **Milad Ashrafizadeh:** Writing – review & editing, Conceptualization. **Gautam Sethi:** Supervision, Formal analysis. **Murtaza M. Tambuwala:** Visualization, Validation, Supervision. **Yuzhuo Wang:** Visualization, Validation, Supervision, Software. **Mohammadreza Ghaffarlou:** Visualization, Validation, Supervision, Software. **Taiwei Jiao:** Writing – review & editing, Conceptualization.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

Acknowledgements

We would like to express our gratitude to Dr. Rupangi Verma from the Medical and Scientific Communication, Research Support Unit at the National University Health System, Singapore for her meticulous review and editing of our manuscript for English language accuracy.

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Further reading

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