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Editorial Board Member of *World Journal of Gastroenterology*, Hideyuki Chiba, MD, PhD, Director, Department of Gastroenterology, Omori Red Cross Hospital, 4-30-1, Chuo, Ota-Ku, Tokyo 143-8527, Japan. h.chiba04@gmail.com

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RESPONSIBLE EDITORS FOR THIS ISSUE

Micelles as potential drug delivery systems for colorectal cancer treatment

Zaynab Fatfat, Maamoun Fatfat, Hala Gali-Muhtasib

Zaynab Fatfat, Maamoun Fatfat, Hala Gali-Muhtasib, Department of Biology, American University of Beirut, Beirut 1107 2020, Lebanon

Hala Gali-Muhtasib, Center for Drug Discovery, American University of Beirut, Beirut 1107 2020, Lebanon

Corresponding author: Hala Gali-Muhtasib, PhD, Professor, Department of Biology, and Center for Drug Discovery, American University of Beirut, Bliss street, Beirut 1107 2020, Lebanon. amro@aub.edu.lb

Abstract

Despite the significant progress in cancer therapy, colorectal cancer (CRC) remains one of the most fatal malignancies worldwide. Chemotherapy is currently the mainstay therapeutic modality adopted for CRC treatment. However, the long-term effectiveness of chemotherapeutic drugs has been hampered by their low bioavailability, non-selective tumor targeting mechanisms, non-specific biodistribution associated with low drug concentrations at the tumor site and undesirable side effects. Over the last decade, there has been increasing interest in using nanotechnology-based drug delivery systems to circumvent these limitations. Various nanoparticles have been developed for delivering chemotherapeutic drugs among which polymeric micelles are attractive candidates. Polymeric micelles are biocompatible nanocarriers that can bypass the biological barriers and preferentially accumulate in tumors *via* the enhanced permeability and retention effect. They can be easily engineered with stimuli-responsive and tumor targeting moieties to further ensure their selective uptake by cancer cells and controlled drug release at the desirable tumor site. They have been shown to effectively improve the pharmacokinetic properties of chemotherapeutic drugs and enhance their safety profile and anticancer efficacy in different types of cancer. Given that combination therapy is the new strategy implemented in cancer therapy, polymeric micelles are suitable for multidrug delivery and allow drugs to act concurrently at the action site to achieve synergistic therapeutic outcomes. They also allow the delivery of anticancer genetic material along with chemotherapy drugs offering a novel approach for CRC therapy. Here, we highlight the properties of polymeric micelles that make them promising drug delivery systems for CRC treatment. We also review their application in CRC chemotherapy and gene therapy as well as in combination cancer chemotherapy.

Key Words: Polymeric micelles; Drug delivery; Colorectal cancer; Chemotherapy; Gene

therapy; Combination cancer therapy

Core Tip: Polymeric micelle-based drug delivery has demonstrated promising therapeutic outcomes against colorectal cancer. These safe nanocarriers exhibit high encapsulation efficiency of chemotherapeutic drugs, improve their water solubility and enhance the stability of nucleic acid-based therapeutics. They also accumulate preferentially at colorectal cancer sites, increase the anticancer effect of the delivered therapeutics and reduce their side effects. Incorporating stimuli-responsive and tumor targeting moieties to their structure further enhances their targeting and therapeutic efficacy. This platform also provides an opportunity to simultaneously deliver different chemotherapeutic drugs or nucleic acid-based therapeutics with chemotherapeutic drugs to the colorectal tumor to achieve an enhanced anticancer response.

INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent cancer and the second leading cause of cancer-related deaths in men and women globally with an estimated 1.9 million new cases and 0.9 million deaths in 2020[1]. These numbers are predicted to reach 3.1 million and 1.6 million, respectively, within the next two decades[2]. The majority of CRC patients present with localized tumors, and nearly 20%-30% of CRC patients have unresectable metastasis[3]. While the 5-year survival rate for localized CRCs is nearly 90%, it is reduced to about 12% for distant metastatic CRCs[4].

Surgery is the primary treatment for patients in early stages of CRC, whereas preoperative or postoperative radiotherapy and chemotherapy are added for patients in advanced stages[5]. Numerous chemotherapeutic drugs, approved by the Food and Drug Administration, have been used for CRC treatment including 5-fluorouracil (5-FU), irinotecan (IRI), oxaliplatin (OXA) and capecitabine[3]. However, their clinical efficacy has been constrained by the adverse side effects and drug resistance that causes cancer relapse and treatment failure[6-8]. To address these drawbacks, combination therapy has been used as an alternative therapeutic approach to cancer monotherapy. Combining therapeutic agents with different modes of action demonstrated great potential in achieving synergistic therapeutic outcomes with reduced side effects in addition to overcoming drug resistance[9]. Several combination chemotherapeutic regimens such as FOLFIRI (folinic acid, 5-FU and IRI), XELOX/CAPOX (OXA and capecitabine) and FOLFOX (folinic acid, 5-FU and OXA) are widely used in clinical treatment for CRC [10]. However, and despite the continued efforts devoted to advance CRC chemotherapy, the prognosis of this disease is still unsatisfactory, particularly for metastatic CRC patients[11].

The main concerns limiting the success of single agent or combination chemotherapy are poor solubility, short half-life, rapid metabolism of the anticancer drugs, lack of selectivity for the tumor sites, non-specific biodistribution and subsequent failure to achieve effective therapeutic concentrations at the action sites[12,13]. Over the past decades, nanotechnology-based drug delivery systems have emerged as a modern approach to overcome these limitations and improve drug performance. They enhance the pharmacokinetic proprieties of the drugs, ensure their delivery to the tumor, prevent toxicity to healthy tissues, increase drug concentration at the tumor site and therefore potentiate their anticancer activity while mitigating their associated side effects[14]. In combination therapy, they can effectively carry several drugs with dissimilar pharmacokinetic profiles and maintain the optimized synergistic drug ratio until they reach the target cancer cells[15]. Additionally, nanosized drug delivery systems opened up new opportunities for the delivery of novel therapeutics along with chemotherapeutic agents, such as genetic anticancer agents, which are considered to be innovative approaches in CRC management [15].

Among the broad range of nanocarriers, polymeric micelles have received particular attention for therapeutic applications in cancer. Many anticancer agents are polycyclic compounds with poor aqueous solubility[16], and polymeric micelles have proven to be powerful vehicles for loading and delivering hydrophobic drugs[17]. Besides being biocompatible and biodegradable, polymeric micelles provide distinct advantages including small size, low-cost, ease of preparation, high drug encapsulation capacity and structural stability[18-20]. They can be easily functionalized with stimuli-responsive and tumor targeting moieties to achieve site-specific delivery and controlled drug release[21]. They also allow the integration of multiple functions other than drug delivery including gene delivery and

imaging[21]. To date, two polymeric micelles, Genexol-PM loading paclitaxel (PTX) and Nanoxel loading docetaxel (DTX), have been approved in Korea and India, respectively, for the treatment of different types of cancer including breast and non-small cell lung cancers[22]. As these nanocarriers have shown therapeutic potential for these solid tumors, they could serve as drug delivery platforms to alleviate the current limitations of CRC chemotherapy and promote the introduction of gene therapy in the management of this disease. Here, we review the composition and characteristics of polymeric micelles in addition to the achievements in micelle-based drug delivery for CRC chemotherapy and gene therapy. Published studies included in this minireview were identified through searching PubMed and Google scholar using different permutations of these keywords "colorectal cancer" or "colon cancer," "chemotherapy" or "gene therapy," "combination" and "micelle." Clinical trials were identified through searching https://clinicaltrials.gov using two keywords "micelle" and "cancer".

## COMPOSITION AND CHARACTERISTICS OF POLYMERIC MICELLES

Polymeric micelles are formed by self-assembly of amphiphilic di-block, tri-block or grafted copolymers in aqueous solutions[23]. Micelles have a two-phase structure including an inner core composed of hydrophobic blocks surrounded by a corona of hydrophilic blocks[24,25]. The widely used core-forming polymers include polyesters, polyethers or polyamino acids, while the most used hydrophilic corona-forming polymer is polyethylene glycol (PEG)[26]. Alternatively, other hydrophilic polymers could be used including chitosan, dextran and hyaluronic acid (HA)[27]. The hydrophilic corona confers steric stability to the micelle, decreases its interactions with serum components and prevents its recognition and early elimination by the reticuloendothelial system, thus enhancing its retention in the systemic circulation[28,29]. The hydrophobic core forms a loading site for lipophilic drugs. It was reported that encapsulating drugs in micelles enhanced their water solubility by 10- to 500-fold[30]. Non-polar drugs can be loaded in micelles by physical entrapment or chemical conjugation[30]. Polymeric micelles used in gene delivery are known as micelleplexes and have cationic properties, which allow the association of nucleic acids *via* electrostatic interactions. The hydrophilic blocks of these micelles are usually composed of polycations including polyethyleneimine (PEI), poly (2-dimethylaminoethyl methacrylate) and polyamino acids[31].

The concentration of copolymers that is needed to form micelles is known as the critical micelle concentration. The critical micelle concentration should be low enough to prevent the dissociation of the micelles upon dilution in the bloodstream[32]. The size of polymeric micelles typically ranges from 10 to 100 nm[33]. Given that nanoparticles that are less than 10 nm can easily undergo renal clearance and those larger than 100 nm can be rapidly eliminated by the liver and spleen, the suitable size of micelles limits their rapid clearance from the circulation[34]. In addition, the nanosize of micelles allows them to passively accumulate in tumor tissues by the enhanced permeability and retention effect[27]. This passive targeting is due to the aberrant and leaky vascular architecture coupled with defective lymphatic drainage that uniquely characterize solid tumors[35]. Being unable to pass through the normal blood vessel walls, the micelles extravasate through the leaky tumor blood vessels, accumulate preferentially at the tumor site and consequently promote the retention of the delivered drug at the tumor tissue[36].

The polymeric micelles deliver the drug payload to the cancer cells by two mechanisms. The therapeutic agents can enter the cancer cell as free drugs after their release from the micelles or be internalized as drugs encapsulated within the micelles to be released within the cell[37]. Chemically conjugated drugs are released by bulk degradation or surface erosion of the micelles, while the physically entrapped drugs are mainly released by diffusion[38]. Intact drug-loaded micelles are internalized *via* cell-dependent pinocytosis, which includes macropinocytosis, clathrin-mediated endocytosis, caveolae-mediated endocytosis and clathrin- and caveolae-independent endocytosis[39-42]. Internalized micelles have been shown to localize in acidic organelles, namely endosomes or lysosomes[40,43]. The loaded drugs were suggested to be released from the micelles in these organelles[40,43] and to subsequently exert their therapeutic effect at the action site[40] (Figure 1).

Active targeting can be used to complement passive targeting for enhanced tumor selectivity, improved cellular uptake and reduced off-target effects[21,23]. The surface of the micelles can be modified with ligands that can specifically recognize and bind to receptors or proteins overexpressed on the tumor cells but that are less expressed on normal cells[44]. Different types of ligands have been conjugated to micelles to ensure their active targeting to cancer cells including antibodies and antibody fragments, proteins including transferrin, peptides such as iRGD, nucleic acid-based ligands such as the AS1411 aptamer and small molecules including folic acid (FA) and HA[45].

Another interesting approach for active targeting is to achieve adequate drug release at the tumor site by designing stimuli-responsive micelles taking advantage of the unique features of the tumor microenvironment. The tumor tissues are characterized by a low pH, upregulation of specific enzymes and elevated levels of glutathione compared with the normal tissues[34]. Stimuli-sensitive polymeric micelles are developed by introducing pH-sensitive linkers in their structures, such as hydrazone bonds or pH-sensitive ionizable functional groups, enzyme-sensitive moieties or redox-sensitive linkers

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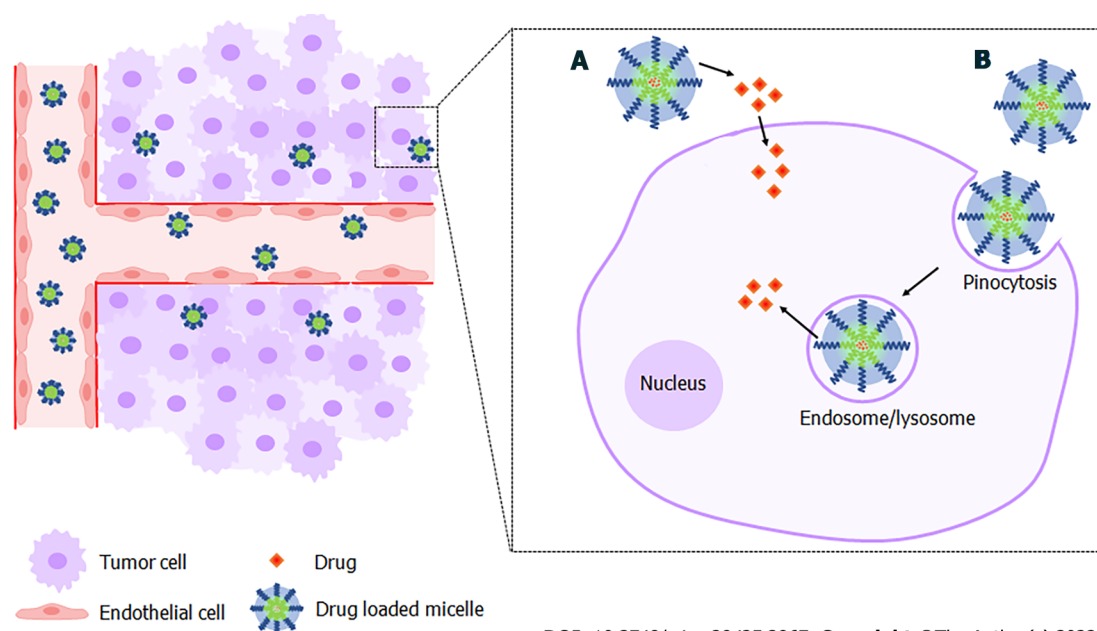
Figure 1 Schematic illustration of the passive targeting of drug formulated micelles to the tumor tissue by enhanced permeability and retention effect and the proposed mechanisms of drug release in the cancer cell. A: The drug can enter the cancer cell in its free form after its release from the micelle; B: The drug can be internalized within the micelle after which it is released in the cancer cell.

including disulfide bonds[34]. When the micelles reach the tumor, the linker degrades in response to the internal stimulus leading to the disassembly of micelles and subsequent drug release[34]. In addition to internal stimuli, polymeric micelles responsive to external stimuli such as magnetic fields, ultrasound and light are designed to achieve a temporal and spatial controlled release of the drug in the desired tumor tissue[34]. After releasing the drug, micelles can dissociate into monomers that are excreted by the kidneys, therefore avoiding any long-term adverse effects[46]. All these properties make polymeric micelles an attractive platform for drug delivery against CRC.

APPLICATION OF POLYMERIC MICELLES IN CRC TREATMENT

The properties and the cellular and molecular mechanisms of action of polymeric micelles used for drug delivery in CRC treatment are presented in Table 1.

Chemotherapy

Numerous studies have demonstrated the potential of polymeric micelles to ensure the targeted delivery of chemotherapeutic drugs to colorectal tumor sites and enhance their therapeutic effectiveness.

IRI is a topoisomerase I inhibitor that is converted by enzymatic activation in the liver and tumors to 7-ethyl-10-hydroxy-camptothecin (SN-38). The latter is about 100-1000 times more potent than IRI against cancer cells[47]. However, only 2%-5% of the administered dose of IRI is converted to SN-38 in the clinic[48]. Although SN-38 demonstrated effective anticancer activity, its direct use as a free drug in the clinic was limited by its hydrophobicity[49]. To circumvent this problem, Koizumi *et al*[50] conjugated SN-38 to PEG-poly(glutamic acid) copolymer with a phenyl ester bond to develop SN-38-loaded polymeric micelles (NK012). The micelle formulation of SN-38 demonstrated extended blood circulation compared with free IRI in mice bearing CRC xenografts. It also prolonged and improved the distribution of SN-38 in the tumor and produced stronger antitumor activities compared to free IRI. To test the correlation between the efficacy of micellar drugs and tumor hypervascularity and hyperpermeability, the effect of NK012 and free IRI was tested in a vascular endothelial growth factor (VEGF)–secreting tumor model namely SBC-3/VEGF. Interestingly, NK012 was found to improve the accumulation and the antitumor activity of SN-38 in SBC-3/VEGF tumors compared to SBC-3/Neo tumors. This was due to the high vascular density and permeability induced by VEGF. However, treatment with free IRI neither significantly increased SN-38 concentration in SBC-3/VEGF tumors nor effectively suppressed tumor growth[50].

Doxorubicin (Dox) is an anthracycline antibiotic that is commonly used to treat several types of solid cancer. However, its clinical use is hampered by dose-dependent cardiotoxicity due to its nonspecific biodistribution[51]. Recently, Brunato *et al*[52] developed methoxyPEG (mPEG)-polyamino acid based

Table 1 Overview of micelles used for drug delivery in colorectal cancer treatment, their characteristics and cellular and molecular mechanisms of action

Block copolymer	CMC	Size in nm	Zeta potential in mV	Entrapment efficiency in %	Therapeutic agent	Cell line or animal model	Cellular and molecular mechanisms of action of micelles loaded with the therapeutic agents	Ref.
PEG-poly (glutamic acid)	N/A	20	N/A	N/A	SN-38	WiDR, SW480, Lovo and HT-29 human colon cancer cells; Female BALB/c nude mice subcutaneously injected with HT-29 cells		Koizumi *et al* [50]
mPEG5kDa-b-[(Dox-hydGlu)$_6$-r-Leu$_{10}$]	4.6 ± 0.2 μmol/L	29.2 ± 1.1	3.61 ± 0.28	N/A	Doxorubicin	CT26 murine colorectal cancer cells; BALB/c mice subcutaneously injected with CT26 cells	(1) Do not cause hemolysis; (2) Do not induce a significant increase of the levels of blood markers for organ toxicity AST, BUN and CPK; and (3) Induce a slight increase of ALT and LDH	Brunato *et al* [52]
PEG-poly (L-lactate-co-hexamethylene-co-adipate) (PEG-PLLHA) and FA-PEG-poly (hexamethylene adipate-co-hexamethylene 2-hydroxyl succinate)	3.65 μg/mL	215.6 ± 3.1	−2.4 ± 0.2	82.1 ± 0.6	Docetaxel	CT-26 cells; Female BALB/c mice subcutaneously injected with CT-26 cells	(1) Induce a more severe tumor necrosis compared to their non-targeted counterparts; (2) Do not cause hemolysis or erythrocyte agglutination; (3) Do not induce histological damage to the major organs of the treated mice; (4) Induce a slight increase of BUN levels; and (5) Do not affect the concentrations of ALT, AST, ALP, and CRE	Su *et al* [54]
PEG-poly (D,L lactate-co-hexamethylene-co-adipate) (PEG-PDLLHA) and FA-PEG-poly (hexamethylene adipate-co-hexamethylene 2-hydroxyl succinate)	3.50 μg/mL	245.5 ± 4.3	−2.8 ± 0.1	79.9 ± 1.0				
D-α-tocopherol succinate (TOS)-conjugated-hyaluronic acid	N/A	95.5 ± 13.7	N/A	90	Paclitaxel	CT26 mouse colon carcinoma cells; NIH-3T3 mouse embryo fibroblasts; HT29 and Lovo human colorectal adenocarcinoma cells; BALB/c mouse subcutaneously injected with CT26 cells	(1) Induce early and late apoptosis in HT29 and Lovo cancer cells *in vitro*; and (2) Induce apoptosis and decrease tumor cell proliferation *in vivo*	Zhu *et al* [58]
mPEG-PCL and DOTAP	N/A	144.8	46.4	N/A	Bcl-xl siRNA and Mcl1 siRNA	C26 cells; BALB/c mice inoculated with C26 cells		Lu *et al* [59]
mPEG-PCL and DOTAP	N/A	46.4 ± 3.7	44.1 ± 1.5	N/A	Plasmid pVAX1-mIL22BP expressing murine IL-22BP	C26 *Mus musculus* colon carcinoma cells; 293t human embryonic kidney cells; BALB/c mice intraperitoneally injected with C26 cells	(1) Induce apoptosis *in vitro*; (2) Decrease the microvessel density characterized by CD31 positive staining; and (3) Induce lymphocyte infiltration in tumor microenvironment as indicated by the detection of CD8+	Men *et al* [60]

							and CD4+ cells in the tumor tissues	
mPEG-PCL and DOTAP	N/A	46 ± 5.6	41.8 ± 0.5	N/A	Plasmid pcDNA-Survivin-T34A expressing Survivin-T34A	C-26 murine colon adenocar-cinoma cells; BALB/c mice intraperitoneally injected with C-26 cells		Duan *et al*[61]
PEI-deoxycholic acid	N/A	88.4 ± 16	N/A	N/A	XIAP siRNA and paclitaxel	HCT-116 human colorectal cancer cells; Male BALB/c nu/nu mice subcutaneously injected with HCT-116 cells		Jang *et al*[63]
PEI-poly (DL-lactic acid)	0.1167 mg/mL	235 ± 25	−22	100	Survivin shRNA and camptothecin	C26 and CHO cells; Female BALB/c mice subcutaneously inoculated with C26 cells	(1) Induce a more pronounced apoptosis *in vitro* compared with their non-targeted counterparts; and (2) Have a lower accumulation in vital organs *in vivo* compared with their non-targeted counterparts	Sanati *et al*[64]
PDMA-b-PCL and mPEG-PCL	N/A	222.1	21.1	N/A	SN-38, USPIO and VEGF siRNA	LS174T human colon adenocar-cinoma cells; Female BALB/c athymic nu+/nu+ mice subcutaneously injected with LS174T cells		Lee *et al*[66]
PEI-poly (D,L lactide) and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-mPEG	N/A	171.25 ± 4.70	15.12 ± 0.36	81.25 ± 3.12	miRNA-34a and irinotecan	CT-26 murine colon adenocar-cinoma cells; Female BALB/c mice injected with CT-26 cells	(1) Upregulate miR-34a and reduce the expression of Bcl-2 and the phosphorylation level of mTOR; (2) Negligible hemolytic activity; and (3) Do not significantly alter the levels of ALP, ALT, ALB, AST, CK, LDH, BUN and CRE	Li *et al*[67]
PEG-lysyl-(α-fluorenylmethyl-oxycarbonyl-ε-Cbz-lysine)₂	2.6 μmol/L	25.4 ± 0.8	0.519 ± 0.730	N/A	Doxorubicin and dasatinib	HCT-116 human colon cancer cells		Zhang *et al*[69]
Poly {(*N*-methyl-dietheneamine sebacate)-*co*-[(cholesteryl oxocar-bonylamido ethyl) methyl bis (ethylene) ammonium bromide] sebacate}	N/A	230	70	N/A	Doxorubicin and TRAIL	SW480 human colorectal adenocarcinoma epithelial cells; WI38 human lung fibroblasts	Induce caspase-dependent apoptosis	Lee *et al*[70]
Cholesteryl-modified single strand DNA (Chl–ssDNA) and its complementary sequence	249 pmol/L	371.3 ± 3.1	-7.07 ± 2.3	84.9 ± 5.21	Doxorubicin and KLA peptide	C57/BL6 mice injected with C26 cells		Charbgoo *et al* [71]
FA-dextran-paclitaxel	3.1 μg/mL	76 ± 2	-11.2 ± 0.8	N/A	Adjudin and paclitaxel	HCT-8 and HCT-8/PTX cells; Mouse subcutaneously injected with HCT-8/PTX cells	(1) Reduce mitochondrial membrane potential and the levels of ATP; and (2) Do not cause hemolysis	Chen *et al*[72]
Poly-lactic-co-glycolic acid grafted branched PEI	1.32 ± 0.003 mg/mL	137.98 ± 2.13	12.3 ± 0.2	70.38 ± 2.34	5-fluorouracil and methotrexate	HCT 116 colon cancer cells		Ashwanikumar *et al*[73]
mPEG-PCL	56	167.5	-0.11	68.8	Doxifluridine	HT-29 human		Sawdon *et al*

	mg/L				and doxorubicin	colorectal adenocarcinoma cells	[74]
		267.5	1.01	86.3	Doxifluridine and SN-38		
Chitosan-PCL	40 mg/mL	163.7	38.8	N/A	Doxifluridine and SN-38	HT-29 human colorectal adenocarcinoma cells	Wang et al[75]

CMC: Critical micelle concentration; mPEG: Methoxypolyethylene glycol; Dox: Doxorubicin; hydGlu: Acid-γ-hydrazide; Leu: Leucine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BUN: Blood urea nitrogen; CPK: Creatine phosphokinase; CK: Creatine kinase; LDH: Lactate dehydrogenase; FA: Folic acid; ALP: Alkaline phosphatase; CRE: Creatinine; DOTAP: N-[1-(2, 3-dioleoyloxy) propyl]-N, N, N-trimethylammonium methyl sulfate; PEI: Polyethyleneimine; PCL: Poly(ε-caprolactone); ALB: Albumin; siRNA: Small interfering RNA; XIAP: X-linked inhibitor of apoptosis; shRNA: Short hairpin RNA; VEGF: Vascular endothelial growth factor; USPIO: Ultra-small superparamagnetic iron oxide nanoparticles; miR-34a: microRNA-34a; TRAIL: Tumor necrosis factor (TNF)-related apoptosis-inducing ligand; IL-22BP: Interleukin-22 binding protein; mTOR: Mammalian target of rapamycin; SN-38: 7-ethyl-10-hydroxy-camptothecin; N/A: Not available; PEG: Polyethylene glycol; TOS: D-α-tocopherol succinate; PTX: Paclitaxel.

micelles for the delivery and controlled release of Dox in CRC. The hydrophobic block of the copolymer included six glutamic acid-γ-hydrazide and ten leucines. Dox was conjugated to glutamic acid through pH-sensitive hydrazone bond to trigger its release in the acidic lysosomal microenvironment. The release of Dox was faster at pH 5.5, which mimics the lysosomal environment. In addition, the intracellular delivery of Dox by the micelles and its trafficking through the lysosomal compartment of CRC cells, where the acidic environment can induce the cleavage of the hydrazone bond, were confirmed by confocal microscopy. Therefore, encapsulating Dox in the formulated micelles may prevent its undesired release in the bloodstream. Interestingly, Dox-loaded micelles had good tolerability, produced a higher antitumor effect compared to the free drug and had limited toxicity in CRC bearing mice[52].

DTX is a microtubule inhibitor that is approved to treat numerous types of cancer. Due to its low water solubility, a mixture of Tween 80 and ethanol is required to solubilize DTX. Yet, Tween 80 used in the available marketed formulation of DTX Taxotere® was associated with adverse effects[53]. Recently, FA-targeted PEG-polyester micelles were formulated for the targeted delivery of DTX against colon cancer. The targeted formulation resulted in an accelerated internalization of the micelles by FA receptor-positive colon cancer cells *in vitro* and in a higher and preferential accumulation of the micelles in colon tumors *in vivo* compared to the non-targeted formulation. Besides being biocompatible and safe, the FA-targeted DTX-loaded micelles exhibited a remarkable 97% tumor-inhibiting efficiency, which was higher than that of non-targeted DTX-loaded micelles (85%) and free DTX (31%) in mice bearing colon tumor xenografts[54].

PTX is a microtubule stabilizing agent commonly used against a variety of cancers including CRC [55]. Because of its low aqueous solubility, Taxol®, the commercial formulation of PTX, uses a nonionic surfactant namely Cremophor® EL[56]. However, Cremophor® EL has been associated with serious side effects such as hypersensitivity, nephrotoxicity and neurotoxicity[57]. Zhu *et al*[58] developed smart micelles for the targeted delivery and controlled release of PTX in colon cancer. Micelles are made from the self-assembly of D-α-tocopherol succinate (TOS) conjugated to HA *via* a redox responsive disulfide bond. Their findings demonstrated that these micelles could specifically accumulate in orthotopic colon tumors and metastatic tumor cells rather than in normal intestinal tissue through binding of HA to CD44 receptors overexpressed on primary and metastatic colon tumor cells. They could also selectively release PTX in orthotopic colon tumors and metastatic tumor cells where the high levels of glutathione break disulfide bonds thus causing drug release. PTX-encapsulated micelles induced the highest survival rate (100%) in mice bearing orthotopic colon tumors compared to untreated group (60%) and free PTX (Taxol) treated group (40%). They also suppressed primary colon tumors and metastatic sites in the intestine and decreased metastasis to other organs and to the peritoneum[58].

Gene therapy

Polymeric micelles were also reported to successfully deliver anticancer genetic material to CRC. Cationic hybrid micelles composed of amphiphilic cationic lipid N-[1-(2,3-dioleoyloxy) propyl]-N, N, N-trimethylammonium methyl sulfate (DOTAP) and mPEG-poly (ε-caprolactone) (PCL) have been used to deliver genes or small interfering RNA (siRNA) for the treatment of colon cancer in preclinical studies. The cationic hydrophilic head of DOTAP ensures the adsorption of the anionic nucleic acid onto the surface of the micelles *via* electrostatic interaction. These hybrid micelles demonstrated an effective and safe delivery of siRNA targeting colon cancer cells. The micelle-based delivery of siRNA caused inhibition of the two anti-apoptotic genes *Bcl-xl* and *Mcl1*, which consequently induced apoptosis in colon cancer cells *in vitro* and suppressed the growth of colon tumors *in vivo*[59]. In another report, these hybrid micelles were used for the delivery of interleukin-22 binding protein (*IL-22BP*) gene, which is known to play a role in blocking the IL-22/IL-22R1 signal axis involved in tumor growth and

metastasis. The micelle-delivered *IL-22BP* gene was efficiently expressed in colon tumors *in vivo* leading to the inhibition of the growth of abdominal cavity metastases. Its anticancer mechanism involved blockage of IL-22, induction of apoptosis and anticancer immune response in addition to inhibition of angiogenesis[60]. In a study conducted by Duan *et al*[61], these hybrid micelles were found to efficiently deliver the classic suicide gene survivin-T34A that acts as a competitor in the survivin pathway involved in apoptosis inhibition[62]. The survivin-T34A gene-loaded micelles inhibited the proliferation of colon cancer cells *in vitro* and the growth of abdominal metastatic colon cancer and malignant ascites *in vivo* by inducing apoptosis[61]. Importantly, in all these studies, this micellar carrier did not induce any pathological changes in the vital organs of the mice with colon cancer.

Combination of chemotherapy with gene therapy

The micellar dual delivery of chemotherapeutic drugs with agents targeted against specific genes have been shown to produce synergistic therapeutic responses against CRC. Cationic micelles based on PEI-deoxycholic acid conjugates have been used for the co-delivery of PTX and siRNA targeting the X-linked inhibitor of apoptosis gene to CRC. The micellar co-delivery of siRNA targeting X-linked inhibitor of apoptosis gene and PTX effectively decreased the expression of X-linked inhibitor of apoptosis at the mRNA and protein levels *in vitro* and *in vivo*. In addition, it was more potent than PTX-loaded micelles as it caused a greater reduction in cell viability of CRC cells and inhibited the growth of colorectal tumors *in vivo*[63]. In another study, Sanati *et al*[64] synthesized cationic micelles for the targeted dual delivery of camptothecin (CPN), a topoisomerase inhibitor, and short hairpin RNA targeting survivin to colon cancer. These micelles containing PEI-poly (D,L-lactic acid) copolymers were coated with polycarboxylic acid dextran and were subsequently modified with AS1411 aptamer that has high affinity for the nucleolin receptors expressed on the surface of colon cancer cells. Cell surface nucleolin expression is known to be more elevated in cancer cells than in normal cells[65]. The conjugation of AS1411 aptamer on the micelles improved their cellular internalization through nucleolin-mediated endocytosis *in vitro* and enhanced their accumulation in colon tumors *in vivo* in comparison with their non-targeted counterparts. While the non-targeted micellar formulation of each of CPN and short hairpin RNA targeting survivin exhibited 3% and 5% tumor inhibitory effect *in vivo*, the targeted and non-targeted formulations of the combination of CPN and short hairpin RNA targeting survivin exerted 93% and 87% tumor inhibitory effects, respectively. It is important to note that the free CPN did not have any anticancer effects *in vivo,* and its micellar formulation prevented the development of its associated systemic toxicity[64]. Moreover, Lee *et al*[66] designed theranostic micelles from cationic PDMA-b-PCL and mPEG-PCL polymers for the combined delivery of SN-38, siRNA targeting human VEGF in addition to a magnetic resonance imaging contrast agent namely ultra-small superparamagnetic iron oxide nanoparticles. The SN-38/ultra-small superparamagnetic iron oxide nanoparticles/siRNA-loaded mixed micelles were targeted passively to colorectal tumor regions *in vivo.* They induced a synergistic tumor growth suppression and allowed the tracking of anticancer effects by magnetic resonance imaging during the treatment[66]. Additionally, hybrid micelles co-self-assembled from PEI-poly (D,L lactide), and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-mPEG were used to deliver IRI and tumor suppressive microRNA-34a (miR-34a) to colon cancer. The micellar co-delivery of the two therapeutic agents showed higher efficacy in inducing apoptosis and inhibiting migration of colon cancer cells *in vitro* compared with free IRI and the single agent formulation. The micellar IRI and miR-34a combination also accumulated in colon tumors *in vivo* and showed superior tumor growth inhibition with low acute systemic toxicity compared with free IRI and the micellar formulation of individual agents[67].

Combination cancer chemotherapy

For dual combination therapy, the encapsulation of drugs in a micellar system could be performed in two ways (Figure 2). In the first method, both drugs are physically loaded in the micelles by hydrophobic interactions. Alternatively, one hydrophobic drug is conjugated to the amphiphilic copolymer, which self-assembles and forms prodrug micelles to subsequently encapsulate the second hydrophobic drug in its core[68].

The chemotherapeutic drug Dox and the tyrosine kinase inhibitor dasatinib were effectively co-encapsulated in the inner hydrophobic core of micelles formed by PEG-peptidic conjugate namely PEG-lysyl-(α-fluorenylmethyloxycarbonyl-ε-Cbz-lysine)₂. The dual drug-loaded micelles exhibited greater inhibition of colon cancer cell proliferation compared with the micellar formulation or the free form of individual drugs[69]. In another study, Dox was co-delivered with the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in cationic micelles to CRC. The micelles were prepared with poly {(*N*-methyldietheneamine sebacate)-*co*-[(cholesteryl oxocarbonylamido ethyl) methyl bis(ethylene) ammonium bromide] sebacate. Dox was encapsulated in the micelles, whereas TRAIL was complexed onto their surface. The internalization of these micelles by CRC cells was mediated by the death receptors expressed on the cell surface. Compared to the formulation of single agents, Dox and TRAIL-loaded micelles enhanced the inhibition of CRC cell viability, the increase of sub-G1 population and the reduction of long-term survival and clonogenicity of cancer cells after the treatment. Interestingly, these remarkable anticancer effects were reported in both TRAIL sensitive and resistant CRC cells. In addition, the cytotoxic effect of the co-loaded micelles was selectively higher against cancer cells than
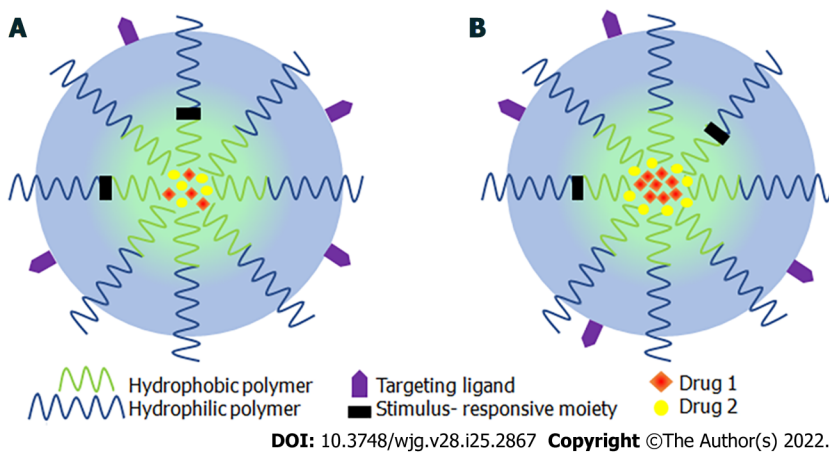
Figure 2 Polymeric micelles for dual drug delivery. A: Both drugs are physically loaded in the core of the micelle; B: One hydrophobic drug is conjugated to the amphiphilic copolymer forming the micelle and the second is encapsulated in its core.

normal cells. This was suggested to be due to the relative disparities in expression levels of decoy and death receptors between normal and cancer cells[70]. A third study reported the combined delivery of Dox and the proapoptotic cationic peptide KLA using DNA micelles. These micelles were made using cholesteryl-modified single strand DNA and its complementary sequence to which the KLA peptide was conjugated. The cationic peptides enhanced the stability of the micelles by protecting them from digestion by nucleases. Since oligonucleotides cannot cross cell membranes, DNA micelles were conjugated to a mucine1 aptamer to target mucine1 receptors overexpressed on the surface of cancer cells. These micelles were found to specifically bind to the mucine1 receptors overexpressing cells and to accumulate within them. The co-delivery of KLA and Dox using the targeted micelles potentiated the inhibition of colon tumor growth *in vivo* compared to free Dox in addition to attenuating its toxic effects [71]. A recent study reported the formulation of a folate receptor-targeted and redox-responsive micellar system for the co-delivery of PTX and adjudin (ADD), a mitochondrial inhibitor, to reverse multidrug resistance in colon cancer. In this drug delivery system, PTX was conjugated to dextran *via* a disulfide bond to form the PTX prodrug, and FA was conjugated to the side chain of dextran-PTX. The resulting PTX prodrug micelles were further used to encapsulate ADD in its hydrophobic core. *In vitro* studies showed that conjugation of FA to the surface of these micelles enhanced their internalization by PTX resistant CRC cells overexpressing the FA receptor. They also demonstrated that ADD inhibited PTX efflux, which consequently improved intracellular accumulation of PTX and therefore its cytotoxic activity. In addition, PTX and ADD-loaded micelles exhibited a prolonged circulation in the blood compared with free PTX *in vivo*. They also increased the concentrations of drugs in resistant colon tumors compared to their non-targeted counterparts and free PTX. Importantly, they demonstrated a strong tumor growth inhibition owing to the active tumor-targeting, the co-delivery of two therapeutic drugs and glutathione-responsive drug release[72]. In another study, micelles engineered with poly-lactic-co-glycolic acid grafted branched PEI were used to co-deliver 5-FU and methotrexate (MTX), which is an antagonist of FA and is known to have anticancer effects against different types of neoplasm. MTX was conjugated to the copolymer forming the prodrug micelles, which was further used to encapsulate 5-FU. In addition to its therapeutic potential, MTX has structural similarity with FA and can therefore act as an FA receptor targeting agent. The conjugation of MTX to the micelles improved their internalization by colon cancer cells compared to the non-conjugated micelles. The combined drug-loaded micelles were more effective in attenuating the viability of colon cancer cells compared to free 5-FU or the micellar MTX[73]. Doxifluridine, a prodrug of 5-FU, has been commonly used in cancer treatment to circumvent the toxicity of 5-FU. Doxifluridine is converted into toxic 5-FU by endogenous thymidine phosphorylase in cancer cells[74]. In a study conducted by Wang *et al*[75], doxifluridine was conjugated to PCL to form a hydrophobic segment that was grafted with hydrophilic chitosan. The produced polymeric prodrugs self-assembled into micelles used for SN-38 encapsulation. The dually loaded micelles were found to reduce the viability of colon cancer cells *in vitro* to a greater extent than doxifluridine-loaded micelles. In another study, doxifluridine-PCL hydrophobic segment was grafted with mPEG to form prodrug micelles serving as carriers to further encapsulate Dox or SN-38. The micellar co-delivery of doxifluridine with Dox or SN-38 exhibited superior inhibition of CRC cell viability with respect to doxifluridine-loaded micelles[74].

Polymeric micelles in clinical trials

Despite their promising potential in preclinical studies against colon cancer, few polymeric micelles have reached the clinical setting. A phase I clinical trial of NK012 was conducted in Japan with a total of 24 patients with solid tumors including 12 patients with CRC. NK012 was found to be well tolerated at

doses up to 28 mg/m^2 when administered every 3 wk. None of the CRC patients had a partial response. However, 5 CRC patients with a history of treatment with OXA and IRI had stable disease; 4 of them received the NK012 regimen for six cycles of treatment or more[76]. Subsequently, the efficacy and safety of NK012 was evaluated in a phase II clinical trial at an initial dose of 28 mg/m^2 in 58 Japanese patients with unresectable metastatic CRC who had been treated with OXA-based chemotherapy. Administration of NK012 resulted in a response rate similar to that of free IRI. In addition, febrile neutropenia and grade ≥ 3 neutropenia were reported in these patients suggesting that an initial dose of 28 mg/m^2 of NK012 may be too high. Further studies should be conducted to determine the optimal dose of NK012 and improve its efficacy and safety[77]. In another study, a phase I clinical trial of NK105, PTX-loaded micelles, was conducted with 19 patients with advanced solid tumors including 1 patient with colon cancer. NK105 was well tolerated, and the recommended phase II dose was determined to be 150 mg/m^2 every 3 wk. The colon cancer patient was reported to have a stable disease for longer than 4 weeks at the time of the completion of the study[78]. Two additional clinical trials on polymeric micelles in CRC were launched but their results have not been reported yet. The first is a phase I clinical trial that aims to determine the maximum tolerated dose/recommended phase II dose of the combination of NK012 with 5-FU and leucovorin in patients with CRC (NCT01238939)[79]. The second is a phase II clinical trial that aims to investigate the safety and the diagnostic performance of ONM-100, a polymer micelle covalently conjugated to an intraoperative fluorescence imaging agent indocyanine green, for the detection of cancer in patients with solid tumors including CRC patients undergoing routine surgery (NCT03735680)[80].

CONCLUSION

Polymeric micelles are potential candidates for delivery of chemotherapeutic drugs and therapeutic genetic material in single or combination treatment against CRC. Polymeric micelles exhibit a safe profile, help in solubilizing hydrophobic chemotherapeutic drugs and achieve prolonged and stabilized drug circulation in the blood. They also promote the passive accumulation of drugs at CRC sites, potentiate their anticancer activity and reduce their unwanted side effects. Conjugating polymeric micelles with stimuli-responsive and tumor targeting moieties further increases their internalization by cancer cells, thus achieving selective drug release at colorectal tumor sites and enhancing drug anticancer effects. In addition, polymeric micelles ensure an effective and safe delivery of genetic material to modulate the expression of apoptotic players in CRC. Co-delivering genetic anticancer agents with chemotherapeutic drugs using micellar systems is known to augment the therapeutic outcome of the latter and therefore represent a promising combination strategy for combating CRC.

This nanocarrier system also allows the incorporation of imaging agents with therapeutics and offers great potential to achieve tumor diagnosis, in addition to tracking the delivery and release of the therapeutic agent and evaluating its therapeutic performance. Although most of the studies evaluating polymeric micelle-mediated combination chemotherapy in CRC were performed *in vitro*, they yielded interesting results. The delivery of drug combinations using polymeric micelles could further intensify their inhibitory effects against CRC and help overcome drug resistance. However, further pharmacokinetic and pharmacodynamic studies are needed prior to the clinical translation of drug-loaded polymeric micelles. Few polymeric micelles have been used in the clinical setting for CRC treatment and diagnosis with promising outcomes, thus their application merits further investigation.

FOOTNOTES

ORCID number: Zaynab Fatfat 0000-0003-1254-0648; Maamoun Fatfat 0000-0001-9642-6708; Hala Gali-Muhtasib 0000-0001-6840-3015.

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