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REVIEW

Application of liposomes in drug development – focus on gastroenterological targets

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Jian-Xin Zhang[1]
Kun Wang[1]
Zheng-Fa Mao[1]
Xin Fan[1]
De-Li Jiang[2]
Min Chen[2]
Lei Cui[1]
Kang Sun[1]
Sheng-Chun Dang[1]

[1]Department of General Surgery, the Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu Province, People's Republic of China; [2]School of Chemistry and Chemical Engineering of Jiangsu University, Zhenjiang, Jiangsu Province, People's Republic of China

Abstract: Over the past decade, liposomes became a focal point in developing drug delivery systems. New liposomes, with novel lipid molecules or conjugates, and new formulations opened possibilities for safely and efficiently treating many diseases including cancers. New types of liposomes can prolong circulation time or specifically deliver drugs to therapeutic targets. This article concentrates on current developments in liposome based drug delivery systems for treating diseases of the gastrointestinal tract. We will review different types and uses of liposomes in the development of therapeutics for gastrointestinal diseases including inflammatory bowel diseases and colorectal cancer.

Keywords: liposome, colorectal cancer, inflammatory bowel disease, drug delivery

Introduction

Dysregulation of the mucosal immune system is thought to be the cause of inflammatory bowel diseases (IBD), with ulcerative colitis (UC) and Crohn's disease (CD) as the two major forms. IBD has been identified as a major risk factor for colitis associated colorectal cancer (CRC).[1–4] The immune system consists of innate immunity and adaptive immunity. Innate immunity provides a limited but quick response to infections while adaptive immunity develops a slower but highly specific immune response and provides immunological memories.[5] Both types of immunity contribute to the pathogenesis of IBD. Defects in innate immunity increase the incidence of IBD[6,7] and different T cell subpopulations are aberrantly activated in CD and UC.[8]

Chronic inflammation may trigger dysplasia by inducing genetic and epigenetic changes in intestinal epithelial cells.[9–13] Once initiated, the fate of dysplastic cells is determined by the balance between the effect of growth factors and cytokines and the subset of immune cells that is activated.[14] It is thought that the Th1 immune response can prevent tumor progression and induce cell death, while Th2 and Th17 responses promote cell proliferation and tumor progression.[14,15]

Diseases of the gastrointestinal (GI) tract, including IBD and CRC, present challenging targets for drug delivery, particularly by the oral route, as minimal systemic absorption and maximal intestinal wall drug levels are desired.[16] The GI tract itself presents a harsh environment for medicines, for example, changing pH, various enzymes, the immune response, first pass liver metabolism, intestinal permeability, and interaction with food/mucus. Nonspecific drug absorption and clearance require higher doses which may result in higher toxicity.

Recent advances in nanotechnology research opened up a vast potential for developing efficient drug delivery systems for GI targets. As a type of nanoparticle,

Correspondence: Sheng-Chun Dang; Jian-Xin Zhang
Department of General Surgery, the Affiliated Hospital of Jiangsu University, Zhenjiang 212001, Jiangsu Province, People's Republic of China
Tel +86 511 8508 2208
Fax +86 511 8882 0988
Email dscgu@163.com; zhangjx@ujs.edu.cn

liposomes have increasingly become an important tool for developing targeted delivery of therapeutics or imaging contrast agents in specific targets to minimize side effects and improve therapeutic effects.[16,17] Liposomes are artificially prepared lipid bilayer vesicles that encapsulate an aqueous phase in which drugs, nutrients, or imaging enhancing agents can be stored. They are nontoxic, nonhemolytic, and nonimmunogenic.[16] Conventional liposomes are composed of only natural phospholipids which are absorbed and cleared by the reticuloendothelial system in vivo and have relatively low stability in vitro. Enormous efforts have been dedicated to improve the characteristics and functionality of liposomes. This review will focus on recent advancements in developing liposome based drug delivery systems for GI diseases.

Application of liposomes in treating intestinal inflammatory diseases

IBD, characterized by chronic inflammation of the gut mucosa, is manifested as either CD or UC. Macrophages and dendritic cells downregulate neutrophil infiltration to confer a protective role during the development of acute colitis.[18] Data has shown that Th1 related cytokines (eg, tumor necrosis factor, interferon-γ, and interleukin [IL]-12) as well as Th17 associated cytokines (eg, IL-17A, IL-21, IL-23) are significantly increased in inflamed mucosa of CD, whereas Th2 cytokines such as IL-5 and IL-13 are upregulated in inflamed areas of UC.[19–21]

It is well documented that CD40/CD40L interaction plays a critical role in both the humoral and cellular immune response as well as in the pathogenesis of IBD.[22] Anti-CD40 and anti-CD40L antibodies are efficient in relieving inflammation, such as in colitis, but severe side effects prevent their use for treatment.[23–25] A charge reversible liposome encapsulated CD40 antisense oligonucleotide has shown great potency in supressing colitis in animals and significantly reduced T lymphocyte activation and proinflammatory cytokine secretion.[26,27] Local administration of cationic liposomes complexed with IL-4 and IL-10 genes was expected to reduce inflammation in patients with severe IBD of the rectum and avoid toxic systemic side effects.[28] Transferrin (TF) and its receptor (TfR) were shown to be overexpressed in inflamed colonic mucosa.[29,30] Tirosh et al reported that negatively charged liposomes bound to TF in an acidic environment of inflamed colon mucosa[29] and anti-TfR antibody conjugated liposomes significantly improve the accumulation of immunoliposome in the mucosa of dinitrobenzensulfonic acid (DNBS) induced rat,[30] which provides a target and potential drug delivery strategy to treat UC.

Chronically elevated radical oxygen species levels are an important element in inducing inflammation in the intestinal mucosa and in the pathogenesis of IBD.[31] Cationic liposomes increased residence time and uptake of superoxide dismutase (SOD) and the SOD mimic tempamine by colonic cells in vitro and in ex vivo models.[32] Anionic liposomes were able to deliver SOD, tempamine, and catalase to inflamed rat intestinal mucosa and achieved longer residence time and better uptake for targeted treatment of UC.[33] Carnitine loaded liposomes were able to correct butyrate metabolism in colonocytes in a DNBS induced rat colitis model.[34] These liposomal agents were able to inhibit local oxidative stress and reduce mucosal inflammation.

Helicobacter pylori infection represents a risk factor for adenomatous polyps and adenocarcinoma of the colon caused by chronic inflammation[35] and *H. pylori* poses an increasing challenge to the clinical management of the infection.[36] An intravenous injection of clodronate liposomes inhibited expression of macrophage related cytokines, reduced *H. bilis* colonization, and *H. bilis* induced typhlocolitis by depleting macrophages in a $Rag2^{-/-}$ mouse model.[37] Clodronate containing liposomes were also effective in protecting against intestinal mucosal injury caused by severe acute pancreatitis in rats.[38] A double liposome based dual drug (amoxicillin and ranitidine bismuth citrate) system showed prolonged sustained drug release, efficient binding to *H. pylori*, enhanced bacterial growth inhibition, antisecretory, and ulcer protective ability in vitro and in vivo.[39,40]

These promising effects of liposomal formulated agents on treating intestinal inflammation or *Helicobacter* infection were obtained from in vitro or animal models (Table 1). It remains extremely challenging to develop new efficient and safe medications for treating intestinal inflammation even with advances in liposome and other nanoparticle research.

Liposomal development and application for GI cancers

CRC is ranked second for both new cancer cases and cancer related deaths in the United States.[41] Limiting the systemic toxic side effects of conventional chemotherapeutic agents is a difficult challenge for new CRC (and other cancers) drug development. Proper liposomal formulation was able to increase anticancer efficacy and reduce drug related toxicity in human gastric and CRC bearing mouse models, which opened new avenues for developing more efficient and safer drugs for GI cancers.[42–44]

Within a short period of time since liposomes were first described, liposome production has evolved from simple

Table 1 Liposomes developed for gastrointestinal diseases other than cancer

Liposome type	Payload	Experimental model	Reference
Amphoteric	CD40 antisense oligonucleotide	Balb/c TNBS-induced colitis	26
Anionic	SOD, TMN, catalase	Rat TNBS-induced colitis	33
Anti-TfR conjugated	None	Rat TNBS-induced colitis	30
Cationic	IL-4 and IL-10 gene	Severe IBD patients	28
Cationic	SOD, TMN	HT-29 cells and rat colon sac	32
Charge reversible	CD40 antisense oligonucleotide	Rat TNBS-induced colitis	27
Double liposome	Amox and RBC	*H. pylori*	40
Liposome	Carnitine	Rat TNBS-induced colitis	34
Liposome	Clodronate	Rag2$^{-/-}$ Balb/c, *H. bilis*	37
Liposome	Clodronate	Rat Sap-induced intestinal mucosal injury	38
Negatively charged at low pH	None	Rat TNBS-induced colitis	29

Abbreviations: *H, Helicobacter*; IBD, inflammatory bowel disease; IL, interleukin; Rag2, recombination activating gene 2; RBC, ranitidine bismuth citrate; SAP, severe acute pancreatitis; SOD, superoxide dismutase; TfR, transferrin receptor; TMN, tempamin; TNBS, 2,4,6-trinitrobenzene sulfonic acid.

naked liposomes (Figure 1A) to stealth (Figure 1C) and/or actively targeted liposomes (Figure 1D, 1E) with variable lipid components, triggering mechanisms (Figure 1B), and conjugating molecules.[45] The advancement in preparing new types of liposomes has helped research in developing new therapeutics for GI cancers (Table 2). Liposomal curcumin was found to be a potent antitumor agent which effectively inhibited the proliferation of SW-620 human CRC cells.[46] Liposomal formulation of different anticancer agents was able to sensitize human CRC cells to thermotherapy and thermochemotherapy[47] or reverse drug resistance in these cells.[48] Using natural unsaturated and hydrogenated phosphatidylcholines, liposomes with a high content of paclitaxel (PTX) were produced and showed lower acute toxicity and higher efficacy against human cancer in animal models when compared with Taxol.[49] The combination of a liposomal anticancer drug with other drugs in free or liposomal form has shown very promising synergistic anticancer activity[50,51] but a combination of liposomal fluoroorotic acid and liposomal irinotecan failed to show, in the C26 tumor mouse model, the synergistic activity observed in C26 cells in vitro,[51] highlighting the challenge of designing multidrug treatments based on in vitro cytotoxicity results. Successful Phase II trials of liposomal drugs in treating advanced CRC or gastric cancer[52,53] provide confidence for research into designing new liposomes with different components or new liposomal drug formulations for GI cancer drug development.

Hybrid liposomes

First developed by Ueoka et al, hybrid liposomes were prepared by simple sonication of a mixture of phospholipids and a surfactant in buffer solutions.[54] Hybrid liposomes composed of L-a-dimyristoylphosphatidylcholine (DMPC) and polyoxyethylene(n)dodecyl ether ($C_{12}(EO)_n$) were able to inhibit the proliferation of and induce apoptosis in human CRC cells in vitro.[55–57] Intravenous administration of DMPC/$C_{12}(EO)_n$ or DMPC/docosahexaenoic acid hybrid liposomes into a liver metastases mouse model of xenografted human CRC exhibited significant therapeutic effects.[58–60] Hybrid liposomes preferentially accumulated into cancer cells and triggered cancer cell apoptosis which resulted in the inhibition of hepatic malignant transformation and prolonged survival of CRC mice with liver metastasis. At the same time, these hybrid liposomes did not show detectable toxicity in vivo. The promising therapeutic benefits shown by hybrid liposomes warrant further pharmacokinetic, pharmacodynamic, and toxicity studies, as well as formulations with other anticancer agents.

PEGylated liposomes

To combat the rapid removal of liposomes from the blood circulation, mainly into the liver and spleen by phagocytic cells of the mononuclear phagocyte system, intensive research was undertaken to modify the components of liposomes to increase their bioavailability.[61] Conjugating polyethylene glycol (PEG) to liposomes (ie, PEGylation) reduced phagocytic recognition, improved pharmacokinetics, and increased biological stability.[61] Pegylation of liposomal PTX drastically increased its in vivo stability, delivered significantly more PTX to tumor tissue, and improved PTX anticancer effects in C26 tumor bearing mice.[62] Similarly, PEGylated liposomal formulated mitomycin C lipid based prodrug had a longer half-life, lower toxicity, and higher anticancer potency than conventional chemotherapy when treating gastric, colon, and pancreatic cancers.[43] In other cases, PEG or low-density lipoprotein (LDL) masked liposomal formulations were able to improve therapeutic effects in CRC and other cancer xenograft models[63] or reverse drug resistance.[64]

A large amount of effort has been dedicated to explore the formulation and characterization of PEG liposomal oxaliplatin (L-OHP). In the SW480 human CRC cell line, PEGylated

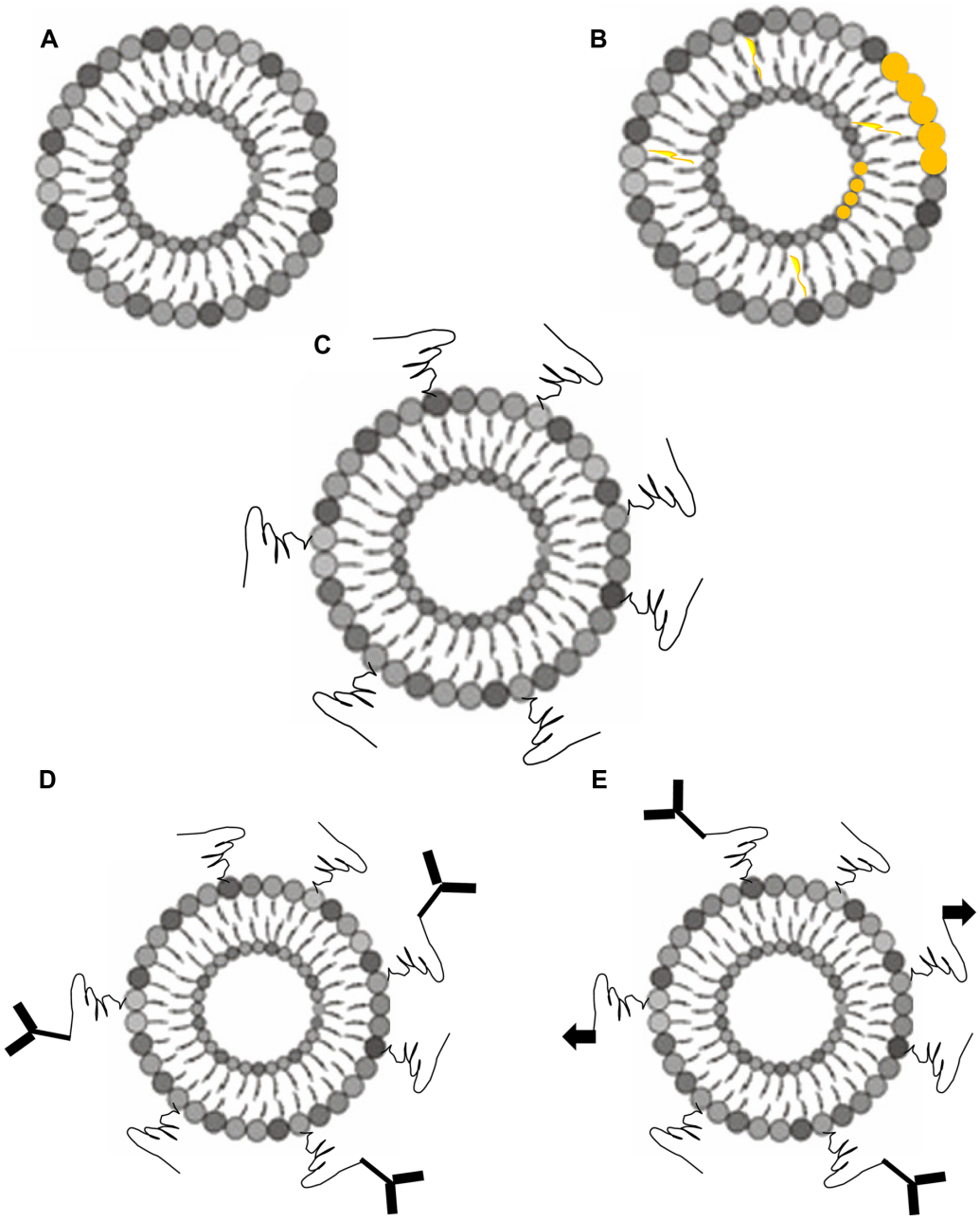

Figure 1 Schematic illustration of major types of liposomes. (**A**) Traditional liposomes; (**B**) liposomes with destabilizing molecules or additional lipid components; (**C**) stealth liposomes; (**D**) stealth liposomes conjugated with targeting molecules; and (**E**) stealth liposomes conjugated with two different targeting molecules.

liposomal L-OHP induced a significantly stronger apoptotic response than the same dose of free L-OHP,[65,66] indicating enhanced anticancer potency of PEGylated liposomal L-OHP. Apoptosis was mediated by Fas/FasL through the caspase 8 pathway[65] and by changing the expression of cyclins and influencing cell cycle arrest.[66] PEG liposomal L-OHP was found to preferably accumulate in tumor tissue after intravenous injection into CRC xenografted nude mice, which promoted antiapoptotic pathways while inhibiting proapoptotic pathways, and resulted in longer survival time.[67] A combination of oral metronomic S-1 dosing with intravenous injection of PEG liposomal L-OHP exerted excellent anticancer efficacy without severe overlapping side effects in a murine CRC model.[68] This combinatory regimen may be an alternative to the current therapeutic regimen for advanced CRC.

Liposomes with triggered drug release

Although pegylation increased the circulation time of liposomes and tumor tissue drug accumulation, cancer cell

Table 2 Liposomes developed for gastrointestinal cancers

Liposome type	Payload	Experimental model	Reference
Anionic	Doxorubicin	HT29 and HT29-dx cells	48
Anti-VEGFR2-PEG	Doxorubicin	HT29-bearing mice	114
Cationic	Temoporfin	COLO206 cells and HT29-bearing mice	85,86
Cationic	Adenovirus-hEndostatin	CT26-bearing mice	116
Cationic	mEndostatin	HCT116 cells and CT26-bearing mice	117
Cationic	FL or FL/TRAIL gene	Lovo cells	118,119
Cationic	Cytosine deaminase gene	HR-8348 human rectal cancer cells and bearing mice	121
DOPC-neurotensin	Doxorubicin	HT29 and TE671 cells	109
Dual	Vinorelbine/indium-111 oxine	HT29/luc mice	93
Hybrid	None	WiDr cells	55
Hybrid	None	HCT116 cells	56,57
Hybrid	None	Liver metastasis of human colon carcinoma mouse models	58–60
LDL-masked	Doxorubicin	HT29 and HT29-dx cells	64
Liposome	Betulinic acid	Nude mice xenografted with human colon and lung cancer tumors	42
Liposome	Curcumin	SW-620 colon cancer cells, A-459 lung cancer cells	46
Liposome	Quercetin	CT26 colon cancer cells and CT26 mouse model	47
Liposome	Paclitaxel	C26 cells and PC14PE6/AS2 bearing mice	49
Liposome	Fluoroortic acid/irinotecan	C26 cells and C26 mouse model	51
Liposome	Aroplatin	Advanced colorectal cancer patients	52
Liposome	Pyropheophorbide-a methyl ester	HCT116 cells	87
Liposome	5,15-diaryl-tetrapyrrole derivative	HCT116 cells	88
Liposome	Par-4 gene	HT29-bearing mice	122
Magnetic	Docetaxel	MKN45-bearing Balb/c/nu/nu mice	79
PEGylated	Mitomycin C	N87 gastric carcinoma (Ca), HCT15 colon Ca, and Panc-1 pancreatic Ca models implanted s.c. in CD1 nude mice	43
PEGylated	Honokiol/cisplatin	C26 mouse model	50
PEGylated	Doxorubicin, 5-fluorouracil and cisplatin or mitomycin-C, 5-fluorouracil and cisplatin	Advanced gastric cancer patients	53
PEGylated	Paclitaxel	C26 bearing mice	62
PEGylated	CKD-602	HT29, A375, ES-2, and H82 tumor xenografted mice	63
PEGylated	Oxaliplatin	SW480	65,66
PEGylated	Oxaliplatin	CRC-xenografted mice	67,68
PEGylated	Indium-111 oxine	HT29/luc mice	92
PEGylated	Indium-111 vinorelbine	CT-26/luc mice	94,95
PEGylated	(111)In-vinorelbine/(188)Re-doxorubicin	C26-bearing mice	100
PEGylated	shRNA anti-kitenin	Colon cancer-bearing mice	120
pH-sensitive	Fe-porphyrin	Gastric cancer cells	75
pH-sensitive	5-fluorouracil	HT-29 cells	76
pH-sensitive-folate	Calcein/cytosine-beta-D-arabinofuranoside	KB human oral cancer cells	77
pH-sensitive-PR_b	Calcein	CT26.WT cells	78
Rhenium-118 labeled	5-fluorouracil	C26/LS-174T colon cancer-bearing mice	96,97
Rhenium-118 labeled	Doxorubicin	C26-bearing mice	98,99
Sterically stabilized	Cisplatin	C26-bearing mice	80
Sulfatide-containing	Doxorubicin	HT-29 xenografted mice	44
TF-PEGylated	None	C26-bearing mice	103
TF-PEGylated	Cisplatin	MKN45P-bearing mice	104
TF-PEGylated	Mercaptoundecahydrododecaborate	C26-bearing mice	105
Thermsensitive	Doxorubicin	C26 tomor-bearing mice	69,70,72
Thermsensitive	Lucifer yellow iodoacetamide	CT26 colon cancer cells and CT26 mouse model	71
Trastuzumab labeled	Docetaxel	NCI-N87 gastic cancer-bearing mice	113

Abbreviations: CRC, colorectal cancer; DOPC, Dioleoylphosphatidylcholine; FL, fms-related tyrosine kinase 3 ligand; LDL, low density lipoprotein; PEG, polyethylene glycol; PR_b, a fibronectin-mimetic peptide; TF, transferrin; TRAIL, tumor necrosis factor (ligand) superfamily, member 10; VEGFR2, Vascular endothelial growth factor receptor 2.

targeting and drug release were still not controlled by PEG liposomes. Efforts have been made to develop liposomes so that drug release is triggered by changes in physical cues.

Thermosensitive liposomes (TSLs) are a promising tool for controlled drug delivery in combination with local hyperthermia. Long circulating TSLs in combination with local hyperthermia was able to deliver two to six times more encapsulated therapeutic or imaging agents to tumor tissue than either liposome alone or free drug, which resulted in inhibited tumor growth and prolonged survival time.[69–71] TSLs can

also be engineered to deliver anticancer drugs to tumor tissue and to carry magnetic resonance imaging agent so that drug release can be monitored by MRI signal intensity after being intravenously injected into C26 tumor bearing mice.[72]

The search for liposomes with increased ability to mediate intracellular delivery of therapeutics resulted in the development of pH sensitive liposomes, which have potential application in treating digestive tract diseases such as some tumors or inflamed tissues that are more acidic than normal tissues.[73,74] Conventional dioleoyl phosphatidylethanolamine (DOPE) based pH sensitive liposomes achieved longer circulation time and tumor targeted delivery by incorporation of PEG.[74] The new generation of pH sensitive liposomes that employ pH sensitive lipids other than DOPE show promise to efficiently deliver anticancer agents to cancer cells.[75,76] Functionalizing pH sensitive liposomes with overexpressed cancer cell surface receptors further enhanced their ability to target cancer cells in a specific manner.[77,78]

There were also attempts to explore other types of liposomes for treating GI cancer to enhance tumor specific drug delivery.[79,80] Injecting docetaxel embedded magnetoliposomes into human MKN45 gastric cancer bearing mice, followed by exposure to an alternating current or magnetic field and local hyperthermia, produced positive results where the amount of drug required for inhibiting cancer growth was greatly reduced, the size of the tumor was decreased, and the survival time was prolonged.[79] Ultrasound was also utilized to trigger cisplatin release from sterically stabilized liposomes and almost 70% of liposomal cisplatin was released in tumor tissue, resulting in tumor regression.[80]

Liposomal formulated photosensitizers and radiochemotherapeutics

Photosensitizers have been used to treat many diseases including brain cancer and lung cancer.[81] Photodynamic therapy has also been intensively studied for the potential treatment of CRC.[82–84] Liposomal temoporfin can selectively target tumor cells with rapid biodistribution and clearance from the blood stream.[85,86] Liposomes encapsulated with novel photosensitizers, such as pyropheophorbide-a methyl ester and 5,15-diaryl-tetrapyrrole derivatives, had significantly higher intracellular drug delivery[87] or more potent cytotoxicity than temoporfin[88] in the HCT-116 CRC cell line. Even with the potential benefits of photodynamic therapy, much work needs to be done before clinical application of liposomal formulation of photosensitizers for CRC treatment is accepted as all work so far has been performed in cell lines.

Molecular imaging is the most common use for nuclear medicine in cancer management[89,90] with a report of cases of radiotherapy.[91] Recently, there has been much effort to progress the investigation of liposome formulation of radiochemotherapeutic and radioimaging agents. Chow et al found that indium-111 ((111)In) labeled oxine delivered by liposomes with a higher concentration of PEG (6 mol%) had a longer circulation time due to reduced phagocytic clearance and enhanced tumor targeting efficiency which resulted in a better therapeutic outcome.[92] Dual liposomes encapsulating vinorelbine and (111)In oxine or PEGylated liposomes encapturing (111)In and vinorelbine had the combined benefits of chemotherapy and radiotherapy.[93–95] Rhenium-188 ((188)Re) labeled PEGylated liposomes carrying anticancer drugs showed the potential benefits of tumor specific drug accumulation and cancer growth inhibition.[96–99] PEGylated liposomes encapsulating (111)Re and vinorelbine was as effective as PEG liposomal (188)Re and doxorubicin for radiochemotherapy of CRC models.[100]

Active targeting liposomes

Passive targeting liposomes were improved to escape reticuloendothelial clearance and increase accumulation in tumor tissues. However, their circulation time and amount of drug targeted to tumors are impacted by every pathophysiological condition of the body. Active targeting liposomes deliver loaded drugs to target cells based on the attachment of specific ligands to the surface of liposomes to recognize and bind to surface markers of pathological cells.[101] TfR is overexpressed in many cancer types so it is an attractive molecule for targeted cancer therapy.[102] TF conjugated PEGylated liposomes possess the advantage of both systems – long circulation capability of pegylation and TfR specific targeting of cancer cells.[103–105] TF PEG liposomes can deliver chemotherapeutic[104] and radiotherapeutic agents[105] specifically into TfR overexpressing cancer cells via receptor mediated endocytosis of liposomes, achieving increased intracellular drug amount, stronger tumor inhibition, and prolonged survival.

The integrin family of cell adhesion proteins play key roles in promoting cell proliferation, tumor angiogenesis, and metastasis.[106] Accordingly, antagonists of several integrins have been investigated as potential therapeutics for cancer and other diseases. After conjugating high affinity integrin $\alpha5\beta1$ and specific binding fibronectin mimetic peptide PR_b, pH sensitive PEG liposomes specifically bind and rapidly release loaded agents into integrin $\alpha5\beta1$ expressing cancer cells.[78]

Neurotensin and neurotensin receptor 1 have been identified as factors promoting tumor growth and cancer metastasis.[107] The selective neurotensin receptor 1 (NTR-1) antagonist sensitized prostate cancer cells to radiation therapy.[108] Functionalization with neurotensin peptides significantly improved the ability of liposomes to deliver chemotherapeutics into CRC cells and resulted in a four fold increase in cytotoxicity.[109] Her2 and VEGFR are overexpressed in many cancer types including gastric cancer[110] and CRC.[111] Anti-Her2 and anti-VEGFR immunoliposomes provide a novel tool for safe and efficient immnochemotherapy of Her2 or VEGFR positive GI cancers.[112–114]

Application of liposomes to gene therapy

Advances in molecular and cellular biology in gene transfer including liposomal formulation of genetic material have made it likely that gene therapy will play an increasingly important role in cancer treatment.[115] Liposome mediated gene therapy can be an independent treatment[116–120] or be used in combination with other treatments.[121,122] Liposome encapsulated endostatin gene suppressed tumor growth and prolonged survival time of human CRC carrying mice and displayed comparable tumor suppressive effects to bevacizumab.[116,117] To avoid the unpredictable side effects of viral vectors, plasmids were evaluated in the liposomal formulation.[118,119,121,122] Liposomal fms-related tyrosine kinase 3 ligand (pEGF-FL) induced cell death in Lovo cells[118] and a combination of FL and tumor necrosis factor (ligand) superfamily, member 10 (TRAIL) genes in cationic liposomes achieved superior anticancer effects than single gene therapy.[119] While overexpressing cancer inhibitors can suppress tumor progression, knockdown of oncogenes with liposomal shRNA would have the same effect. PEG liposome encapsulated shRNA against the kitenin gene inhibited CRC growth in mice and enhanced apoptotic signals.[120] Combined with radiation, liposomal cytosine deaminase gene and 5-fluorocytosine reduced tumor volune more than 80% when compared to control in mice bearing human rectal cancer.[121] Par-4 plasmid delivered by liposomes enhanced 5-fluorouracil induced cancer cell apoptosis,[122] indicating liposome mediated gene therapy combined with chemotherapeutics or radiation can be a safe and efficient treatment for CRC.

Future perspective

In the past decade, advances have been made in generating new types of liposomes and in developing strategies to utilize liposomes in treating GI diseases. Increasing drug accumulation at the target tissue and minimizing systematic side effects are still the biggest challenges in designing new drug delivery systems. As PEGylated liposomes inherit the advantage of prolonged circulating time over conventional liposomes, maximizing the capacity of PEGylated liposomes would be of great interest in future development of drug delivery systems. A combination strategy may be conceived by formulating therapeutics in PEGylated liposomes functionalized with active targeting molecules (such as antibodies, growth factors, peptides, carbohydrates, lipoproteins, etc) for targeted tissue accumulation of drugs and incorporating components sensitive to pH, temperature, light, ultrasound, or magnetism for controlled drug release. Success in developing such combination of liposomes would provide safe and efficient drug delivery for GI diseases ranging from IBD to cancers.

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Disclosure

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