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Review

Drug self-delivery systems for cancer therapy

Si-Yong Qin [a], Ai-Qing Zhang [a], Si-Xue Cheng [b], Lei Rong [b], Xian-Zheng Zhang [b, *]

[a] School of Chemistry and Materials Science, South-Central University for Nationalities, Wuhan, 430074, China
[b] Key Laboratory of Biomedical Polymers of Ministry of Education & Department of Chemistry, Wuhan University, Wuhan, 430072, China

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ABSTRACT

Carrier-assistant drug delivery systems (DDSs) have been rapidly established for cancer therapy and great strides have been made in recent years. However, further development of DDSs is retarded by the aspects such as the low drug carrying capacity, carrier-induced toxicity and immunogenicity, complex synthesis manipulation. Drug self-delivery systems (DSDSs), in which active drugs exhibit nanoscale characteristic to realize intracellular delivery by themselves without the help of nanocarriers, have been rapidly developed to address these issues. In this review, we present a comprehensive summary of the recent advances in DSDSs for cancer therapy. After a brief introduction to the major types of DSDSs and their fabrication strategies, we emphatically discuss some representative achievements of these DSDSs for passive or/and positive targeting therapy, combinational therapy as well as theranostics. The design principle is explained and justified, which can cast a new light on developing drug delivery systems for cancer treatments.

1. Introduction

Cancer is a leading cause of death worldwide. According to GLOBOCAN results, about 14.1 million new cancer cases occurred in 2012 and 8.2 million patients suffered from the cancer-induced death [1]. There has been tremendous progress over the past few decades in cancer therapy. Among various therapeutics, chemotherapy, relying on the high cytotoxicity of chemotherapeutic agents against cancer cells, has become a predominant tactic for most cancer managements due to its high efficiency compared with other treatments. Unfortunately, conventional chemotherapeutic agents always exhibit inherent limitations such as the nonspecific distribution, poor bioavailability, rapid blood clearance and poor solubility in physiological environments [2,3]. Approaches for addressing these issues often relate with the employment of assistant nanocarriers such as self-assembled nanoarchitectures [4–7] and inorganic nano-frames [8,9] for drug delivery, which protect drugs from rapid blood/renal clearance and achieve the preferential accumulation of drugs within solid tumors due to the enhanced permeability and retention (EPR) effect [10,11]. These carrier-assistant drug delivery systems (DDSs) are indeed effective and a few of them have undergone clinical trials [12]. Nevertheless, the requirement associating with large quantities of additional excipients would inevitably result in disadvantages. For example, their drug carrying capacities were not satisfactory (typically below 10% (w/w)) [13,14]. Most carriers for drug delivery are just excipients without direct therapeutic efficacy, which may cause additional short-term or long-term toxicities from their metabolites. Furthermore, some carriers may result in the immune reactions against carriers or therapeutics [15–17]. The undesirable immune response caused by the interaction between carriers and specific cell surface receptors would induce interferon response, cytokine storm and/or lymphocytes activation, which therefore impaired the therapeutic effects [17,18].

Drug self-delivery systems (DSDSs), involving that active drugs exhibit nanoscale characteristic to realize intracellular delivery by themselves without the aid of additional nanocarriers [19], have been proposed as a novel paradigm for high performance cancer therapy. In virtue of bottom-up technique, yielded DSDSs hold the following attractions: (i) customized nanoarchitectures that protect drugs from disruption and facilitate the selective accumulation in tumors due to EPR effect; (ii) excellent drug loading capacities (up to 100% for pure nanodrugs); (iii) the success in avoiding tedious steps for preparing additional carriers and (iv) no carrier-induced toxicity and immunogenicity.

On the basis of those distinctive merits, recent years have witnessed rapid progress in the development of DSDSs for cancer therapy. This review mainly looks at the molecular design,

* Corresponding author.
E-mail address: xz-zhang@whu.edu.cn (X.-Z. Zhang).

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Abbreviations

ACQ	aggregation-caused quenching;
ADDC	amphiphilic drug-drug conjugate
ALPs	alkaline phosphatases
ATO	arsenic trioxide
BdM	bendamustine
BODIPY	boron dipyrromethene
C18PMH-PEG	poly(maleic anhydride-alt-1-octadecene) -polyethylene glycol
Cb	chlorambucil
Ce6	chlorine e6
CLSM	confocal laser scanning microscopy
CPP	cell penetrating peptide
CPT	camptothecin
Cur	curcumin
DDSs	drug delivery systems
DiR	1,1-dioctadecyl-3,3,3,3-tetramethylindotricarbocyanine iodide
DSDSs	drug self-delivery systems
DSPE-PEG-MTX	1,2-distearoyl-sn-glycero-3-phospho ethanolamine-polyethylene glycol-methotrexate
DOX	doxorubicin
DOX·HCl	doxorubicin hydrochloride
DTT	dithiothreitol
EET	electronic energy transfer
EPR	enhanced permeability and retention
FA	folic acid
FdU	floxuridine
FRET	Förster Resonance Energy Transfer
5-FU	fluorouracil
Gem	gemcitabine
GSH	glutathione
HAS	human serum albumin
HCPT	10-hydroxycamptothecin
HeLa	Human cervical carcinoma
H2TPyP	5,10,15,20-tetro (4-pyridyl) porphyrin
Ir	irinotecan
KLA peptide	$(KLAKLAK)_2$-containing peptide
Lac	lactose
LMW	low molecular weight
MDR	multidrug resistance
MMP-7	matrix metalloproteinase-7
MTX	methotrexate
OEG	oligomer chain of ethylene glycol
PCI	photochemical internalization
PEG-PLGA	methoxypolyethyleneglycol-poly(lactic-co-glycolic acid)
PI3K	phosphatidylinositol-3-kinase
PpIX	protoporphyrin IX
PSA	psammaplin A
PTX	paclitaxel
Py	porphyrin
RES	reticuloendothelial system
RGDS	Arg-Gly-Asp-Ser
ROS	reactive oxygen species
SA	stearic acid
SN-38	7-ethyl-10-hydroxy camptothecin
TTZ	trastuzumab
VE	vitamin E

fabrication strategy and therapeutic advantages of DSDSs. These design concepts are originated from elevating the drug loading capacity and/or avoiding the adverse side-effects from additional carriers, with the purpose of optimizing the therapeutic outcomes. By delicate design, multifunctional therapeutic modalities such as targeting therapy, combinational therapy as well as theranostics have been well realized in all-in-one DSDSs. Specially, DSDSs could easily offer a remarkable synergistic anticancer efficiency based on multiple drug delivery.

2. Classification and fabrication strategy of drug self-delivery systems

This term “drug self-delivery systems (DSDSs)” mainly refers to that no additional carriers are used in the process of drug delivery. In some literature, DSDSs are also named as “carrier-free drug delivery systems” since they act as the pilot and the cargo and enable the carrier-free drug trafficking. According to the different therapeutic mechanisms of building blocks, DSDSs are classified into prodrug self-delivery, pure drug self-delivery, therapeutic carrier based self-delivery and non-toxic agent based self-delivery categories. Prodrug self-delivery involves the systems that the active drugs are pre-decorated with small groups *via* cleavable linkers, which could form nanostructures to achieve the self-delivery modality (Fig. 1A). In contrast to prodrug self-delivery systems with fine-tuning to prime drugs, pure drug self-delivery systems are composed of pure drug self-aggregated nanodrugs that achieve the intracellular trafficking (Fig. 1B). A representative example of the pure drug self-delivery systems is drug nanocrystal [20]. Nanosized multidrugs and amphiphilic drug-drug conjugates are also assigned to pure drug self-delivery systems, since these nanodrugs are made of therapeutic components with no or few nontherapeutic ingredients. In therapeutic carrier based self-delivery systems, both the carriers and loaded drugs can act as the therapeutic agents for the combinational therapy. Additionally, some special systems, in which non-cytotoxic agents participate into versatile local delivery and achieve controllable aggregation in/around cancers to induce the cell apoptosis, are reviewed as non-toxic agent based self-delivery systems.

Bottom-up strategy provides a simple and feasible route for preparing DSDSs [21,22], which generates nanoscale drugs from therapeutic agents in aqueous solutions. Depending on molecular self-assembly or/and precipitation procedure, drugs self-assemble or aggregate into nano-objects with customized sizes and shapes (Fig. 1). Originated from their structural amphipathicity, prodrug molecules, drug-drug conjugates and a few free drugs spontaneously self-assemble into well-defined nanostructures for local delivery. Nevertheless, most free anti-cancerous drugs exhibit poor aqueous solubility [23], which poses a challenge to fabricate pure drug self-delivery systems *via* self-assembly strategy.

Precipitation approach as an alternative route is developed to convert hydrophobic pure drugs into nano-objects. During precipitation procedure, free drug is first dissolved with a spot of suitable solvent, which is then injected into aqueous solution to drive pre-dissolved drug molecules to self-aggregate into nanodrugs, leaving part of hydrophilic segment exposed to the aqueous environment. The negligible organic solvent can be removed through dialysis or reserved in the bulk solution. Very recently, a