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The application of prodrug-based nano-drug delivery strategy in cancer combination therapy

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ABSTRACT

Single drug therapy that leads to the multidrug resistance of cancer cells and severe side-effect is a thing of the past. Combination therapies that affect multiple signaling pathways have been the focus of recent active research. Due to the successful development of prodrug-based nano-drug delivery systems (P-N-DDSs), their use has been extended to combination therapy as drug delivery platforms. In this review, we focus specifically on the P-N-DDSs in the field of combination therapy including the combinations of prodrugs with different chemotherapeutic agents, other therapeutic agents, nucleic acid or the combination of different types of therapy (*e.g.* chemotherapy and phototherapy). The relevant examples of prodrug-based nanoparticulate drug delivery strategy in combination cancer therapy from the recent literature are discussed to demonstrate the feasibilities of relevant technology.

Contents

1. Introduction

Cancer is a complex disease that represents one of the leading causes of death in developed countries [1,2]. Although a large number of potent chemotherapeutic anticancer agents have been successfully used in clinical practice, there has been no significant progress in cancer treatment due to the lack of selectivity against cancer cells and associated toxic side effects [1,3,4]. Besides, the multidrug resistance of cancer cells and limited regime of clinical uses of single drug becomes the major limitations in anti-tumor treatment [5]. Therefore, the combination therapy with decreased side effects and improved therapeutic profile has drawn more and more attention from pharmaceutical researchers [6].

Combination therapy, generally refers to either the co-administration of two or more therapeutic agents achieving a synergistic antiproliferative effect or to the combination of different types of therapy (*e.g.* chemotherapy and radiotherapy) [7]. Multi-agent therapy can generate synergistic anticancer effects by focus on different signaling pathways in tumor cells, overcome mechanisms of resistance and minimize side effects [8,9]. Actually, it is routinely used for the treatment of cancer and indeed improves the therapeutic effect [10]. For instance, the combination therapy of doxorubicin (DOX) and paclitaxel (PTX) is used as first-line treatment for metastatic breast cancer [11–13]. The efficacy of hypoxia-activated prodrug TH-302 in combination with doxorubicin for use in first-line advanced soft tissue sarcoma (STS)

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Table 1
Examples of recently developed P-N-DDSs for combination of prodrug plus free drug.

Name	Agent 1 type (name) Agent 2 type (name)	Nanoplatform	Refs.
PluronicF127-CS-DOX + PTX	Doxorubicin (DOX) Paclitaxel (PTX)	Polymeric micelle	[35]
PEGylated Taxol + DOX	Doxorubicin (DOX) Paclitaxel (PTX)	Janus nanogels	[66]
PEG-C6-AZO-CA4 + DOX	Combretastatin A-4 (CA4) Doxorubicin (DOX)	Micelle	[67]
Herparin-DEX + DOX	Dexamethasone(DEX) Doxorubicin(DOX)	Polymeric micelle	[68]
PLGA-PEG-CBP + PTX	Carboplatin (CBP) Paclitaxel (PTX)	Nanoparticles	[36]
5-FU-stearic acid + CDDP	5-FU Cisplatin (CDDP)	Nanostructured lipid carriers (NLC)	[69]
TPGS-cisplatin + docetaxel	Cisplatin Docetaxel	Nanoparticles	[37]
PLA-Pt (IV) + docetaxel	Cisplatin (Pt) Docetaxel	Polymeric nanoparticle	[18]
Pluronic P105-DOX + PTX	Doxorubicin (DOX) Paclitaxel (PTX)	Mixed micelles	[31]
mPEG-*b*-PLG-*g*-PTX + DOX	Doxorubicin (DOX) Paclitaxel (PTX)	Nanoparticles	[70]

CS: chitosan; PEG: polyethylene glycol; C6: hexanethiol; AZO: azobenzene; PLGA: Poly (DL-lactide-*co*-glycolide); TPGS: D-alpha-tocopheryl polyethylene glycol 1000 succinate; PLA: polyactide; mPEG-*b*-PLG: methoxypoly(ethylene glycol)-*block*-poly(L-glutamic acid).

assessed in clinical studies was favorably with outcomes achieved compared with other first-line chemotherapies for advanced STS [14]. Besides, the combination of gemcitabine and TH-302 significantly improved tumor response compared with gemcitabine alone in previously untreated, locally advanced or metastatic pancreatic cancer [15].

Though appropriate drug combinations can produce significant benefits in cancer treatment, current combination approach through the cocktail administration leaves plenty of room for improvements [16]. One major challenge is how to ensure the correct radio of the combined drugs to the target, as the optimized dose ratio complicated by dissimilar pharmacokinetics and biodistribution is hard to be maintained due to different rates of metabolism within the body [7]. Besides, the combination of small molecule drugs would accompany with unfavorable toxic side effects. From this point of view, the application of nanotechnology has opened up unprecedented opportunities in controlled drug delivery and novel combination strategies [16–18]. A myriad of nanoscale drug delivery systems including micelles, liposomes, nanoparticles and nanogels, have endowed encapsulated drugs more favorable pharmacokinetic profiles compared to free small-molecule drugs [5,19]. They solve the shortcomings of most anticancer drugs such as low solubility, fast blood clearance, multidrug resistance, reduce the side effects by the selective accumulation at tumor sites over normal tissues, *via* both passive and active mechanisms [20–23]. They can also improve the efficacy of multimodality treatment by their ability to effectively delivering multiple therapeutic agents simultaneously and to synchronize their delivery to the target site [24]. For example, Zhen Li et al. constructed hollow silica nanoparticles sealed with ZnO quantum dots to co-deliver camptothecin (CPT) and doxorubicin (DOX· HCl) [25]. Only when the nanoparticles entered into the acid intracellular compartments of cancer cells, could the ZnO quantum dots be dissolved and trigger the release of the drug. The pH-sensitive drug release minimized the toxicity for normal tissues. More important, *in vitro* cellular assays revealed that the two drugs combinations with different anticancer mechanism highly improved chemotherapeutic effect [25].

However, in a single combinatorial nanoparticle, drug co-encapsulation through non-covalent physical entrapment leads to poor stability and batch-to-batch inconsistency in drug loading and release kinetics, especially when two drugs have different solubility, charge and molecular weight [26]. It presents a challenge for conventional nanocarriers to co-encapsulate two drugs with different chemical and physical characters and precisely keep the relative dosages of the two drugs, as most nanoparticle-based drug combinations are comprised of bioactive compounds with similar water solubility [16,24,27]. For instance, polymeric micelles are not suitable for loading well water-soluble drugs because of their hydrophobic core, not to mention relative combination therapy [16]. Liposomes are capable of carrying hydrophilic and hydrophobic drugs in its inner core and bilayer membrane, respectively. But this formulation has disadvantages, such as a lower localized hydrophobic drug concentration in the lipid bilayer and a higher initial burst, as well as thermodynamic instability [28].

Prodrugs are defined as chemically modified, biologically inert compounds that are metabolized *in vivo* to regenerate the parent bioactive components [3]. The main advantages of prodrugs compared to the parent free drugs are: (a) improved solubility in water or lipid membrane [29]; (b) decreased adverse effects [30,31]; (c) improved cell uptake [1,3]. By conjugating a polymer or a tumor-specific ligand to chemotherapy drugs *via* a cleavable bond, they can also be designed to target specific antigens or enzymes that are over-expressed on tumor cells compared with other normal cells [1,32]. Recently, their applications have been extended to combination therapy. Prodrug-based nano-drug delivery systems in the field of combination chemotherapy to facilitate more efficient delivery of anticancer drugs are still advanced and pioneering [33].

The aim of this paper is to review the use of prodrug-based nano-drug delivery system strategy in combination therapy with a focus on cancer treatment. We focus separately on each type of systems, including combination therapy of prodrugs with different chemotherapy agents, other therapeutic agents, nucleic acid and the combination of chemotherapy with phototherapy. We also discuss some interesting examples from the recent literature on the development of P-N-DDS strategy in combination cancer therapy.

2. Different chemotherapy drugs combinations

2.1. Prodrug + free drug

In this approach, a prodrug is administered in combination with a low molecular weight drug. It means one free antitumor drug