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Recent advances of cocktail chemotherapy by combination drug delivery systems☆

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ABSTRACT

Combination chemotherapy is widely exploited for enhanced cancer treatment in the clinic. However, the traditional cocktail administration of combination regimens often suffers from varying pharmacokinetics among different drugs. The emergence of nanotechnology offers an unparalleled opportunity for developing advanced combination drug delivery strategies with the ability to encapsulate various drugs simultaneously and unify the pharmacokinetics of each drug. This review surveys the most recent advances in combination delivery of multiple small molecule chemotherapeutics using nanocarriers. The mechanisms underlying combination chemotherapy, including the synergistic, additive and potentiation effects, are also discussed with typical examples. We further highlight the sequential and site-specific co-delivery strategies, which provide new guidelines for development of programmable combination drug delivery systems. Clinical outlook and challenges are also discussed in the end.

Contents

1. Introduction

Cancer is the prominent cause of death worldwide and treatment for cancer remains one of the most challenging problems [1–6]. Current cancer treatments in the clinic mainly rely on surgical intervention, radiation therapy and chemotherapy [7,8]. Surgery remains the main treatment for cancer in which the bulk of the tumor is removed but the peripheral part cannot be completely eradicated due to the poor cellular differentiation in most of tumors [9–12]. In addition, surgery-induced acceleration of tumor and metastatic growth has been concerned, probably caused by inflammatory response during wound healing [13]. On the other hand, chemotherapy provides an essential auxiliary treatment, while the efficacy is far from satisfaction mainly due to the drug delivery problems, including various types of physiological barriers as well as drug resistance [14–18]. Additionally, traditional chemotherapeutic drugs often harm healthy cells and cause toxicity to the patient [19–25].

The drug delivery systems (DDS) are expected to achieve easy drug administration, enhanced drug accumulation at tumor site, minimized side effects and optimized therapeutic efficacy [1,26–30]. By taking advantage of profound understanding of cellular and molecular complexity of cancer and the availability of versatile materials, including

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synthetic polymers [31–34], lipids [35–39], inorganic materials [40–43], and biomacromolecule scaffolds [44–49], the DDS capable of delivering chemotherapeutics to tumor site have been developed enormously [50–54]. The emergence of nanotechnology has made profound impact on combination drug delivery and nanoparticles have been introduced as the drug carriers to achieve efficient chemotherapeutics delivery for decades. Compared with the direct administration of free drugs, encapsulation of drugs in nanocarriers provides distinct advantages, including better drug solubility [55–57], improved pharmacokinetic [58,59] and pharmacodynamic properties [60,61], prolonged circulation time [62,63], minimized side effects [64], and sustained drug release kinetics [65,66]. Furthermore, nanocarriers can protect a drug from quick clearance by evading the reticuloendothelial system; thus a high blood circulation profile enables transport through biological barriers and increases the availability of drug at the targeted disease site [28]. To date, an impressive library of nanoscaled DDS has been designed with varying sizes, architecture and surface physicochemical properties [67–71]. Typical nanocarriers in combination chemotherapy include polymeric nanoparticles [72,73], liposomes [74,75] and inorganic nanoparticles [76,77].

Due to the physiological complexity of the tumor, a single drug or even a stand-alone therapy strategy may not be sufficient for effective treatment [78,79]. Combination chemotherapy, referring to the simultaneous administration of two or multiple therapeutic agents [80–83], is becoming increasingly important for achieving long-term prognosis and decreasing unwanted side effects [84–86]. Unlike monotherapy, combination chemotherapy can modulate different signaling pathways in cancer cells, cause synergetic responses, maximize the therapeutic effect and overcome drug resistance [87,88]. As shown in Fig. 1A, the combination chemotherapy often achieves favorable outcomes through various mechanisms including synergistic effects, additive effects and potentiation effects. The discovery of new drug combinations and the development of novel drug combination systems can be facilitated when the specific mechanisms underlying activities have been fully elucidated. To fulfill effective delivery of multiple chemotherapeutics, the combination DDS can be designed through a variety of strategies (Fig. 1B) (Table 1). Loading of drugs into the nanoparticulate DDS can be achieved via the chemical conjugation, physical encapsulation or the combination of both methods. Partner drug can be covalently conjugated to the matrix and subsequently attached on the surface of drug-loading nanoparticle to form the combination DDS. Additionally, electrostatic interaction can also be applied to assemble combination DDS by taking advantage of opposed charged partner drugs and drugs-loading nanoparticles.

In this review, nanocarrier-based combination delivery of cocktail small-molecular chemotherapeutics will be surveyed. The mechanisms underlying actions and co-delivery strategies for combination therapy, including synergistic combination effects, additive combination effects, and potentiation combination effects, will be summarized in details. We will further introduce the sequential and site-specific co-delivery strategies, which provide new insights for development of programmable combination drug delivery systems. Finally, the future opportunities and challenges of delivery of cocktail chemotherapeutics will be discussed.

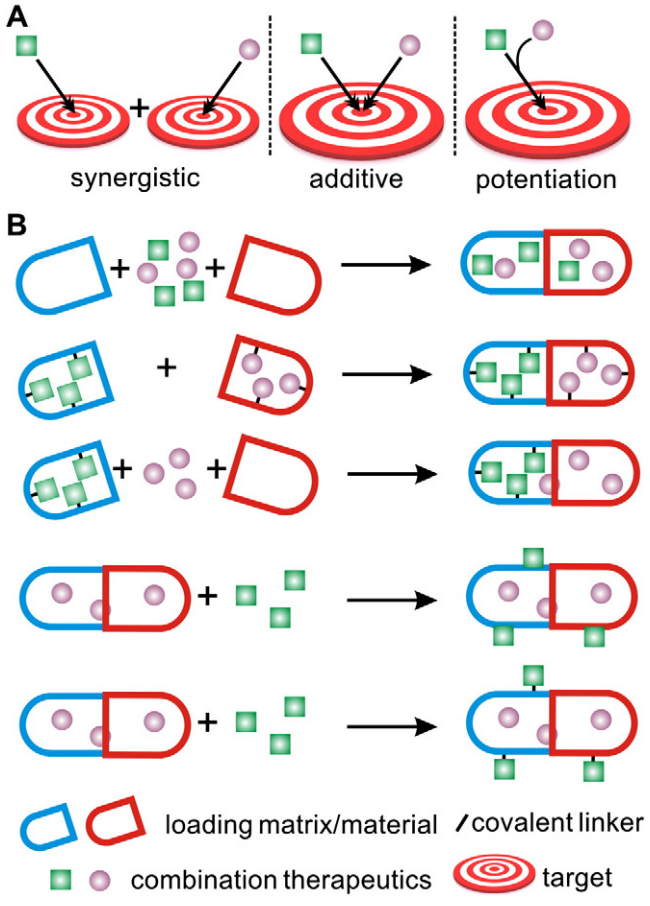

Fig. 1. A. Schematic illustration of the mechanisms underlying combination chemotherapy, including synergistic effects, additive effects and potentiation effects. B. Popular implementations of co-encapsulating small molecular drugs in combination delivery systems. Drugs can be loaded into the co-delivery system through different implementations, including physical encapsulation + physical encapsulation, chemical conjugation + chemical conjugation, physical encapsulation + chemical conjugation, physical encapsulation + absorbance on the surface of formulation, and physical encapsulation + conjugation on the surface of formulation (from top to down). The loading matrices/materials (in blue and red) can be either different or identical.

2. Chemotherapy and combination chemotherapy in cancer

Cancer chemotherapy refers to using chemical substances to treat tumor [9,89]. The history of chemotherapy could be traced back to 1940s when nitrogen mustards and antifolate drugs were first introduced [90,91]. Since then, chemotherapy has played a vital role in the auxiliary treatment of cancer and gained extensive development. However, it is generally accepted that cancer is usually the result of a combination of interconnected disease pathways that may not be treated effectively with a single therapeutic agent or strategy [92–95]. The emergence of drug resistance and tumor recurrence is often associated with the single drug based cancer chemotherapy, mainly due to pathway overlapping [96], cross-talk [97] and neutralizing response [98,99] that commonly occur with cancer monotherapy. Nowadays, the well-established combination therapy for cancer treatment provides effective solutions for the dilemma.

The combination chemotherapy has evolved into a reasonably scientific clinical treatment from the preliminary trials. Several important principles are involved in the combination chemotherapy, including non-overlapping toxicity, non-cross resistance and enhancement of tumor cell killing efficacy [100]. Traditional drug combinations for cancer therapy include methotrexate-based combinations, anthracyline-based combinations and paclitaxel (PTX)-based combinations [101,102]. Methotrexate, an antimetabolite and antifolate drug, is often combined with cyclophosphamide and 5-fluorouracyl (5-FU) for traditional combination chemotherapy due to the capability of inhibiting the metabolism of folic acid [103,104]. Anthracyline-based chemotherapeutics, including daunorubicin, doxorubicin (Dox), epirubicin, idarubicin and valrubicin, play a vital role in combination with cyclophosphamide and 5-FU. Cyclophosphamide inhibits the DNA replication by forming intrastrand and interstrand DNA crosslinking [105], while 5-FU acts as a thymidylate synthase inhibitor to prevent DNA replication [106]. PTX-based combinations are another commonly used traditional chemotherapy. For example, PTX and cisplatin (Pt) were combined for advanced ovarian cancer therapy and PTX was also