Biochemical Pharmacology 83 (2012) 1104–1111

Contents lists available at SciVerse ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

Nanoparticle-based combination therapy toward overcoming drug resistance in cancer

Che-Ming Jack Hu, Liangfang Zhang *

Department of Nanoengineering and Moores Cancer Center, University of California, San Diego, La Jolla, CA 92093, USA

ARTICLE INFO

Article history:
Received 21 September 2011
Accepted 9 January 2012
Available online 18 January 2012

Keywords:
Multidrug resistance
Combination therapy
Therapeutic synergism
Nanoparticle drug delivery
Cancer treatment

ABSTRACT

The use of multiple therapeutic agents in combination has become the primary strategy to treat drug resistant cancers. However, administration of combinatorial regimens is limited by the varying pharmacokinetics of different drugs, which results in inconsistent drug uptake and suboptimal drug combination at the tumor sites. Conventional combination strategies in aim to maximize therapeutic efficacy based on maximum tolerated dose does not account for the therapeutic synergism that is sensitive to both dosing and scheduling of multiple drugs. In the present review, we will discuss the development of multidrug-loaded nanoparticles against drug resistant cancers. Nanoparticle-based combination therapy against experimental multidrug resistant (MDR) cancer models will be summarized. In addition, we will highlight the recent advances in nanoparticle-based combination strategies against clinical cancer drug resistance, including co-encapsulation of drugs with different physicochemical properties, ratiometric control over drug loading, and temporal sequencing on drug release. These emerging strategies promise novel and better tailored combinatorial regimens for clinical cancer treatment.

Contents

1. Introduction

The long-standing challenge in cancer drug resistance and the urgent need for novel combination therapy are highlighted in a recent perspective by Woodcock et al., who liken the complexity of

* Corresponding author at: Department of Nanoengineering and Moores Cancer Center, University of California, San Diego, 3855 Health Sciences Drive, MC-0815, La Jolla, CA 92093-0815, USA. Tel.: +1 858 246 0999; fax: +1 858 534 9553.
E-mail address: zhang@ucsd.edu (L. Zhang).

0006-2952/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2012.01.008

cancer biology to webs of interconnected routes with multiple redundancies [1]. Very tellingly, this analogy points out the inadequacy of single-drug therapy, whose one-dimensional action mechanism often activates and strengthens the alternative pathways, prompting the emergence of chemoresistance mutations and tumor relapse. In aim to increase treatment efficacy, combination chemotherapy has long been adopted as the standard of care against many cancer types. It is generally acknowledged that through the proper drug combination the treatment can promote synergistic actions, improve target selectivity, and deter the development of cancer drug resistance [2].

Despite being a clinical standard, current combination approach through the cocktail administration leaves plenty of room for improvements. While *in vitro* cellular studies have generated many leads for combinatorial regimens, their clinical results are often met with little improvement in efficacy and at times higher toxicity [3,4]. One major factor that separates *in vitro* success from impressive clinical outcomes is the varying pharmacokinetics among different drugs. Upon systemic administration, drugs undergo distinctive physiological fates and non-uniform distribution. Predicting and controlling the therapeutic mixtures that reach the diseased cells and tissues therefore become a major clinical challenge. The common approach based on maximum tolerated dose fails to take into account the intricate pharmacologic interactions that are sensitive to both dosing and sequencing of combinatorial drugs. One strategy toward more effective combination therapies thus is devising a better scheme for precise and controlled delivery of multiple therapeutic agents.

Advances in nanotechnology have opened up unprecedented opportunities in controlled drug delivery and novel combination strategies. Nanoscale particles between 10 and 200 nm in diameters have shown more favorable pharmacokinetic profiles as compared to small-molecule drugs; these drug-loaded nanoparticles exhibit prolonged systemic circulation lifetime, sustained drug release kinetics, and better tumor accumulations through both passive and active mechanisms [5–8]. Recently, nanocarriers are gaining increasing attention for their ability to co-encapsulate multiple therapeutic agents and to synchronize their delivery to the diseased cells. Various nanoparticle platforms such as liposomes, polymeric micelles, dendrimers, and mesoporous silica particles have been used to carry broad classes of therapeutics including cytotoxic agents, chemosensitizers, small interference RNA (siRNA), and antiangiogenic agents. In this review, we will cover several nanoparticulate systems that have been used for co-encapsulation and co-delivery of multiple drugs. We will then summarize nanoparticle-based combination strategies to overcome the experimental models of multidrug resistance (MDR) in cancer. Lastly, in light of the complexity in clinical cancer drug resistance, we will offer insights on emerging features in nanoparticle drug delivery that promise broader applicability and better design for combination therapy. These features include co-encapsulating hydrophobic and hydrophilic drugs, precise and ratiometric control over drug loading, and sequenced drug release.

2. Nanoparticulate systems for combinatorial drug delivery

Nanoparticulate systems such as liposomes, polymeric micelles, and polymer–drug conjugates have led to about two dozen clinically approved therapeutic products [6]. Herein, we highlight the nanocarriers that have been demonstrated to carry two or more types of therapeutic payloads. While these systems share the common aim in promoting synergism through controlled combinatorial drug delivery, each platform has its unique strength and characteristics. The different particle structures, materials, and preparation processes are emphasized here to provide design considerations toward developing combinatorial therapeutics.

2.1. Liposomes

Liposomes are spherical vesicles consisting of amphiphilic phospholipid bilayers. Phosphatidylcholine and phosphatidylethanolamine are the common building blocks for liposomal preparation whereas cholesterol is a frequent additive that serves to modify the rigidity of the lipid membranes. Liposomes are typically prepared by rehydrating lipid films to form multilamellar vesicles (MLV), which subsequently undergo mechanical extrusions to form unilamellar vesicles [9]. The resulting structure contains a lipid bilayer and an inner aqueous core, which are capable of carrying lipophilic and hydrophilic drugs, respectively.

Liposomal drug loading can be accomplished either through active extrusion or through passive diffusion. In the active extrusion approach, drugs are suspended along with the phospholipids in aqueous solution. The resulting mixture of MLV and drugs are then extruded through membrane with defined pore size to form drug-loaded liposomes. In the passive diffusion approach, liposomes are first prepared and then mixed with solubilized drugs. These drug molecules then enter the liposomes by diffusing through the lipid bilayers. Multidrug-loaded liposomes can be prepared using either of the loading schemes followed by filtration of unloaded drugs. For instance, in preparing CPX-351, a combinatorial liposome for leukemia treatment, cytarabine is hydrated and extruded with the lipid components yielding cytarabine-loaded liposomes. These liposomes are then incubated with daunorubicin to achieve dual-drug encapsulation [10]. Currently liposomes are the only nanoparticle-based combinatorial drug delivery platform that has entered clinical trials.

2.2. Polymeric nanoparticles

In contrast to liposomal vehicles that carry drug cargoes in their aqueous cavity, polymeric nanoparticles contain a solid, polymer-filled core that is better suited for water-insoluble drug payloads. The solid structure also gives polymeric nanoparticles higher stability, more sustained and controllable drug release profiles, and more uniform size distribution. Polymeric nanoparticles are typically prepared through the self-assembly of amphiphilic diblock copolymers. A variety of polymers have been used to prepare polymeric nanoparticles, including biodegradable synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) and natural polymers such as polysaccharides and polypeptides [11–13]. In general, drug encapsulation into polymeric nanoparticles is achieved by mixing the drugs with the polymer solution. As the polymers self-assemble into particles, they physically entrap the drug compounds. Multiple hydrophobic therapeutic compounds have been loaded simultaneously through this physical entrapment approach. Other encapsulation schemes have taken advantage of the synthesis flexibility in the polymeric building blocks. Through drug–polymer conjugations and particle functionalization, more advanced combinatorial drug encapsulation schemes have been developed to extend compatibility to hydrophilic drugs [14–16], precisely controlled drug loading ratios [17], and fine tuned drug release sequence and kinetics [18,19].

2.3. Polymer–drug conjugates

Covalently attaching therapeutic agents to water-soluble polymers is another approach that improves the drugs' systemic circulation lifetime and reduces their exposure to normal tissues. Many low-molecular-weight anticancer drugs such as paclitaxel, doxorubicin (DOX), and camptothecin have shown improved pharmacokinetic profiles and clinical efficacy following polymer