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Review article

Chemotherapy agent-unsaturated fatty acid prodrugs and prodrug-nanoplatforms for cancer chemotherapy

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ABSTRACT

Unsaturated fatty acids (UFAs), with the distinct advantages of good biocompatibility and innate tumor-targeting effect, have been widely investigated for the rational design of chemotherapy agent-unsaturated fatty acid (CA-UFA) prodrugs in cancer therapy. Among them, several CA-UFA prodrugs have successfully entered clinical trials and are promising prospects for potential clinical applications. In addition, CA-UFA prodrug-based nanoparticulate drug delivery systems (nano-DDS), which integrate the advantages of CA-UFA prodrugs and nano-DDS, have been emerging as versatile nano-carriers for the efficient delivery of chemotherapeutics. In this paper, we review the advanced drug delivery strategies based on UFA conjugates and focus on the recent advances in CA-UFA prodrugs and the emerging CA-UFA prodrug-based nano-DDS. First, we discuss the rational design of CA-UFA prodrugs in response to the multiple obstacles in chemotherapy, with particular emphasis on the latest progress in both preclinical studies and clinical trials. Moreover, the emerging CA-UFA prodrug-based nano-DDS are also addressed. Finally, the prospects and potential challenges of CA-UFA prodrug-based drug delivery strategies in chemotherapy are highlighted.

1. Introduction

Cancer is a severe disease threatening human health around the world [1,2]. Despite great efforts over the last few decades, the current state of cancer therapy is still far from satisfactory [3]. Among all the therapeutic options, chemotherapy is one of the most effective strategies for treating various types of tumors, especially advanced and metastatic tumors [1]. Unfortunately, traditional chemotherapeutics exhibit a high toxicity profile with a narrow therapeutic window, leading to limited efficiency and serious adverse effects [2,4]. In addition, the chemotherapeutic efficacy of anticancer drugs is greatly limited by multidrug resistance [1,5].

As shown in Fig. 1, in response to these challenges in cancer therapy, a series of strategies have been developed for the high-efficiency delivery of chemotherapeutics, including the prodrug strategy and nanoparticulate drug delivery systems (nano-DDS) [6,7]. Prodrugs usually refer to pharmacologically inactive substances in vitro that can be readily converted into their active parent drugs in vivo [3,4]. A successful prodrug strategy can effectively address the inferior properties of parent drugs, such as poor water solubility, low permeability, chemical instability, poor pharmacokinetic characteristics and severe toxicity [4,8]. In addition, benefiting from the rapid development of biomaterials and nanotechnology, nano-DDS have shown distinct advantages in anticancer drug delivery, including improved drug availability, prolonged systemic circulation time, increased tumor accumulation, and spatiotemporally controlled drug release [1,7,9]. Furthermore, prodrug-based nano-DDS, which integrate the advantages of both strategies into one single nano-platform, have been developed for effective drug delivery and has distinct advantages in terms of high drug loading, enhanced stability, and reduced toxicity [3].

Unsaturated fatty acids (UFAs), which contain at least one unsaturated double bond in the alkyl chain, are a main ingredient of human fat [10,11]. Distinguished by the numbers of double bonds, UFAs can be divided into monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) [12]. As shown in Fig. 2, typical MUFAs include oleic acid (OA) and elaidic acid (EA), which contain one double bond in the alkyl chain [13]. PUFAs usually contain 18–22 carbon atoms, such as arachidonic acid (AA), docosahexaenoic acid (DHA), conjugated linoleic acid (CLA), eicosapentaenoic acid (EPA), linoleic acid (LA), and linolenic acid (LNA) [14]. In addition, according to the site of the first double bond in the alkyl chain, PUFAs are usually divided into two categories: omega-3 and omega-6 fatty acids (Fig. 2) [15,16]. Although most PUFAs are of great importance to physiological function, they cannot be synthesized by the body and only come from

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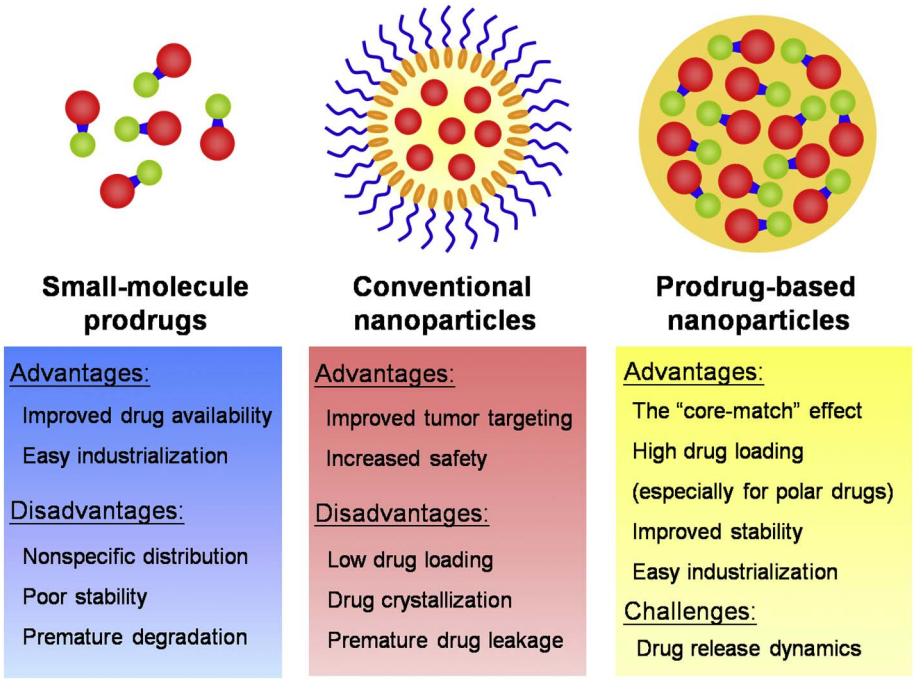

Fig. 1. Strategies to improve the delivery efficiency of anticancer drugs: prodrugs, conventional nano-DDS and prodrug-based nano-DDS.

the diet [17]. Therefore, PUFAs are also usually called "essential fatty acids" [18]. As showed in Fig. 3, UFAs have many important physiological functions for human beings: (i) UFAs are essential for the normal functions of the biomembrane [18]; (ii) UFAs are important in the cardiovascular health by reducing the contents of cholesterol and triglycerides in blood and lowering blood viscosity [15]; (iii) UFAs show anti-inflammatory effects by modulating the expression of pro-inflammatory cytokines (e.g. interleukins 1 and 6) [19,20]; (iv) UFAs are also involved in the synthesis of some endogenous substances, such as prostaglandin and thromboxane [21]; and (v) UFAs can promote brain development by increasing the activity of brain cells, e.g., DHA and EPA [16,22]. In addition to the abovementioned important physiological functions for human health, UFAs have also been found to show certain antitumor activities and the ability to increase the chemotherapeutic sensitivity of anticancer drugs, showing great potential in cancer therapy [14,18,23–26]. In addition, UFAs show natural tumor-targeting properties due to the high nutrient demand required maintain the uncontrollable growth of tumor cells [24,25].

Benefiting from their good biocompatibility, innate tumor-targeting properties and potential pharmacological activities in cancer treatment, UFAs are ideal candidates for the design of high-efficiency drug carriers in cancer treatment. As a result, a large number of chemotherapy agent-unsaturated fatty acid (CA-UFA) prodrugs have been developed for chemotherapy in the last few decades (Table 1). Among them, three promising CA-UFA prodrugs have successfully entered clinical trials, including gemcitabine-elaidic acid conjugate (CP-4126), cytarabine-elaidic acid conjugate (CP-4055) and paclitaxel-DHA conjugate (PTX-DHA). In addition, CA-UFA prodrug-based nano-DDS have also been emerging as a promising platform for the efficient delivery of chemotherapeutics, including prodrug-encapsulated nanosystems and prodrug-based self-nanoassemblies. Although great progress has been made in the field of CA-UFA prodrug strategies, to the best of our knowledge, no attention has been paid to outlining the research progress. The present article summarizes the development of CA-UFA prodrug strategies in cancer therapy. First, the rational design of CA-UFA prodrugs in response to the delivery obstacles of anticancer drugs are discussed, with special emphasis on the clinical trials and the latest preclinical studies. Furthermore, the recent progress of high-efficiency CA-UFA prodrug-based nano-DDS is also addressed. Finally, the developmental prospects and potential challenges of CA-UFA prodrug-

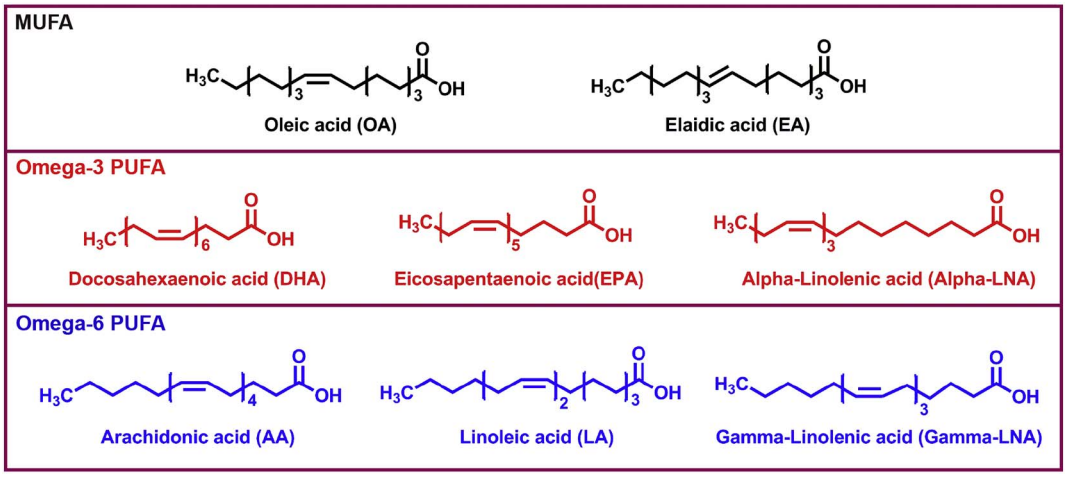

Fig. 2. Chemical structures of several typical unsaturated fatty acids (UFAs): MUFAs, Omega-3 PUFAs and Omega-6 PUFAs.