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Sensitizing nanoparticle based platinum(IV) drugs by curcumin for better chemotherapy

Xiang Kang[a,1], Chen Zhao[b,1], Lesan Yan[c,d,*], Ruogu Qi[c,d,*], Xiabin Jing[c], Zehua Wang[a]

[a] Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
[b] Department of Medicine, Mount Sinai Roosevelt, 1000 Tenth Avenue, Suite 3A-02, New York, NY 10019, United States
[c] State Key Laboratory of Polymer Physics and Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, China
[d] The University of Chinese Academy of Sciences, Beijing 100049, China

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ABSTRACT

A polymer-cisplatin(IV) conjugate was prepared by attaching Pt(IV)-COOH to a biodegradable amphiphilic block copolymer containing pendant OH groups. The conjugate can assemble into micelles (M(Pt)) with a mean diameter of ca. 169 nm. Further, curcumin (CM) was used to sensitize platinum drug based nanoparticles to overcome cisplatin resistance and enhance antitumor efficacy. *In vitro* studies showed that M(Pt)/CM combinations had great synergistic effect both on cisplatin sensitive and cisplatin resistant cell lines (A2780 and A2780DDP). *In vivo* studies showed that M(Pt)/CM had a much lower systemic toxicity and an enhanced antitumor efficacy compared to cisplatin alone or the corresponding cisplatin/CM combinations. Therefore, polymer-cisplatin(IV) conjugate with small molecules that serve as a non-cytotoxic or minimally cytotoxic sensitizer or enhancer provide a promising strategy, which may have potential clinical implications in the near future.

1. Introduction

Curcumin (diferuloylmethane) is a phytochemical that has a wide range of therapeutic activities and has potent anti-proliferative effects against a variety of tumors *in vitro* [1–3]. Curcumin has been found to interact with a wide variety of cell signaling proteins, down-regulated transcription factors, and multidrug resistance (MDR) proteins [4–8]. Curcumin has further been shown to impact tumor growth *in vivo*, decrease cellular invasion, and potentiate radio- and chemo-therapies [9–12].

Platinum(II) complexes have been used as anticancer drugs for a long time. Among them, cisplatin has proven as a highly effective chemotherapeutic agent for treating various types of cancers. The application of platinum(II) complexes is limited by the presence of side effects including nephrotoxicity, ototoxicity and irreversible peripheral nerve damage [13–15]. Some tumors are intrinsically resistant to platinum-based drugs, while other tumors acquire resistance after initial treatment. Intrinsic or acquired resistance, as well as the formidable side effects caused by accumulating platinum in normal tissues, often hampers Pt-based treatment of cancer. Therefore, new platinum-based anticancer drugs that overcome these challenges have long been a major pursuit for researchers around the world. Among them, relatively inert formulations of platinum(IV), such as JM216, have been considered in anticancer applications. Moreover, Pt(IV) complexes can be reduced to yield platinum(II) species to exhibit anti-cancer activities in the intracellular environment through reductive elimination of the axial ligands [16–18].

Curcumin has potential anticancer effects through multiple signaling pathways [19]. Increasing evidence indicates that curcumin reverses chemo-resistance and sensitizes cancer cells to chemotherapy and targeted therapy in cancer cells [20]. Chemopreventative phytochemicals which have antitumor and antioxidant properties may overcome problems of chemoresistance [21]. Nonspecific toxicity towards normal cells is associated with platinum-based chemotherapy against cancer. These agents can exert effects by targeting numerous cellular proteins that in turn affect multiple steps in pathways leading to tumourigenesis. Chirnomas and colleagues studied the interaction of cisplatin and curcumin in several cancer cell lines [22]. Results showed that curcumin, a compound that is generally regarded as safe, can sensitize

* Corresponding authors at: State Key Laboratory of Polymer Physics and Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, China.
E-mail addresses: lesanyan@gmail.com (L. Yan), Ruoguqix@gmail.com (R. Qi).
[1] These authors contributed equally to this work.

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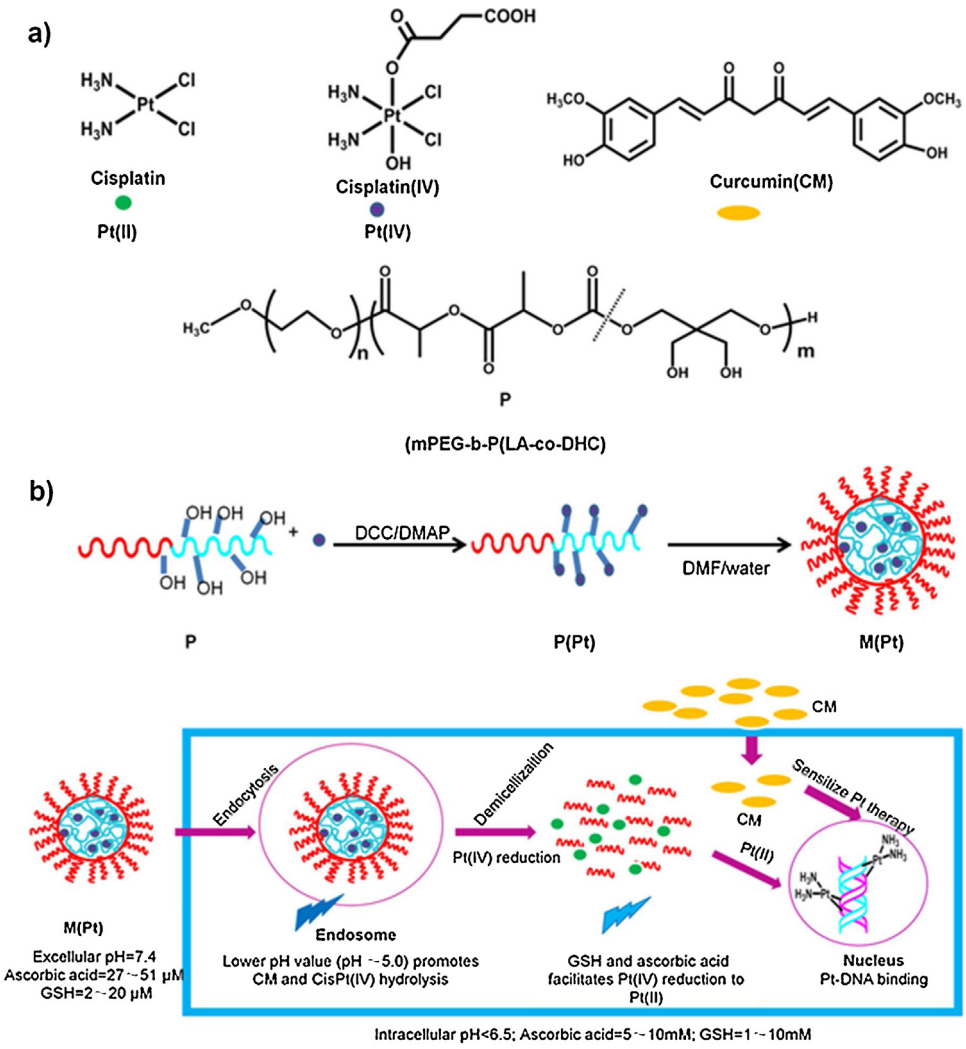

Scheme 1. (a) Molecular formulas for cisplatin (Pt(II)), cisplatin(IV) (Pt(IV)), curcumin (CM), and molecular structure of mPEG-b-P(LA-co-DHC); (b) Preparation of P(Pt) and M(Pt), and possible mechanism of action of M(Pt) combined with curcumin.

ovarian and breast tumor cell lines to cisplatin and lead to cell death through apoptosis. In addition, Huq and colleagues investigated the synergy of platinum drugs and a number of tumor-active phytochemicals including curcumin [23]. The degree of synergism has been found to be high.

Ovarian cancer is the most common cause of death from gynecologic malignancy and it is the fifth-leading cause of cancer-related death [24]. The agents used for chemotherapy in ovarian cancer have shifted over time from alkylating agents to combination therapies of platinum-based chemotherapies and taxane compounds [25]. While modern nanotechnology provides the possibility of targeting and delivering genes/drugs for treating cancers via polymers, lipid, inorganic nanoparticles [26–30], fully overcoming the drug resistance is still not achieved in most cases. Researchers around the world have found that curcumin has an anti-tumor and anti-metastasis effect [20,21]. Combination curcumin and cisplatin leads to the benefit of reversing the drug resistance [31]. Bearing these in mind, we propose and implement a new strategy to sensitize a polymer-platinum(IV) pro-drug with the small molecule curcumin in order to overcome the resistance of human ovarian cancer. We used the A2780 (cisplatin sensitive) and A2780DDP (cisplatin resistant) cell lines based on their unique properties and availability. As shown in Scheme 1, polymer conjugates of cisplatin(IV) (abbreviated as P(Pt)) were synthesized by coupling cisplatin(IV) (Pt(IV)) to biodegradable polymer carriers. We used a micelle-based approach to accommodate platinum(IV) (abbreviated as M(Pt)). Our *in vitro* work reveals the synergistic effect of M(Pt) with the small molecule curcumin was similar to that of cisplatin and curcumin. *In vivo*, we show that M(Pt) in combination with curcumin was much more effective in antitumor effects than cisplatin or curcumin alone. While typical combination therapies rely on the interaction between two strongly cytotoxic agents, we have shown that the combination of a polymer drug with a small molecule, one of which is a non-cytotoxic or minimally cytotoxic sensitizer or enhancer, is a feasible strategy. Our approach leads not only to enhanced antitumor efficacy but also to reduced systemic toxicity compared to non-combination formulations of the main cytotoxic drug. Because safety and efficacy are two primary considerations for clinical use, such combination strategies may have potential clinical implications in the near future.

2. Materials and methods

2.1. Materials

N,N-dicyclohexylcarbodiimide(DCC) and 4-dimethylaminopyridine (DMAP) were purchased from Sigma-Aldrich. Curcumin was purchased from Aladdin (Shanghai).