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The inhibition of tumor growth and metastasis by self-assembled nanofibers of taxol

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ABSTRACT

Molecular hydrogels have big potential for local delivery and sustained release of therapeutic agents. In this paper, we reported on a molecular hydrogel mainly formed by the widely used anti-cancer drug of taxol. The hydrogel was formed by an ester bond hydrolysis process from a taxol derivative (Taxol-SA-GSSG, **1**) and could be administrated into solid tumors to dramatically hinder their growths and prevent their metastasis. Besides the improved anti-cancer effect compared to the clinically used intravenous (i.v.) injection of Taxol®, the concentration of taxol in blood was low due to the local administration of taxol hydrogels, which greatly enhanced the dosage tolerance of mice to taxol and might reduce side effects of taxol during chemotherapy. Our observations suggested that the hydrogel mainly composed of taxol would have great potential for its practical applications.

1. Introduction

We reported on a molecular hydrogel mainly formed by clinically used taxol without any chemical modifications. In order to overcome the shortcomings of anti-cancer drugs during chemotherapy (e.g. low water solubility and systemic toxicity), great efforts have been applied for the development of drug carriers that can improve the solubility of widely used anti-cancer drugs (e.g. taxol, camptothecin, and doxorubicin) and specifically deliver these drugs to cancer cells [1–6]. Besides the widely used polymeric hydrogels [7,8], nano-sized carriers such as liposomes, vesicles formed by DNA and block co-polymers and some inorganic materials [9–14], self-assembled molecular hydrogelators exhibited great potential for targeted or local delivery of hydrophobic anti-cancer drugs [15]. Stupp group have used a self-assembled peptide amphiphile to deliver Camptothecin to reduce the size of tumor [16], Pochan and co-workers also applied a peptide-based molecular hydrogel for local delivery of curcumin for chemotherapy [17], and John group have successfully constructed molecular hydrogelators by enzymes and developed enzyme-responsive hydrogels for the delivery of hydrophobic drug molecules [18,19]. Besides using molecular gelators as carriers for the delivery of anti-cancer drugs, Xu and our groups have recently reported several gelators based on taxol conjugates and these hydrogels of taxol derivatives might be developed into novel self-delivery systems for sustained release of taxol (gelators served as both carriers and delivered components) [20–22]

Though molecular hydrogels have shown promising potential for the delivery of anti-cancer drugs, the reported delivery systems are either with carriers (self-assembled molecules) or formed by drug derivatives, which need long time and cost more to evaluate the compatibility of carriers or compatibility and efficacy of drug derivatives. Actually, the only two FDA approval drug delivery systems of molecular hydrogels are those formed by therapeutic agents themselves (Lanreotide and Degarelix) without any chemical modifications [23,24]. Overall, molecular hydrogels formed by therapeutic agents themselves should have bigger potential for practical applications than other delivery systems with molecular hydrogels. In this paper, we reported on a molecular hydrogel mainly formed by taxol itself for local (intra-tumor (i.t.)) delivery of taxol with improved anti-tumor efficacy and lower systemic toxicity.

2. Materials and methods

2.1. Formation of hydrogel and its recovery property

20.0 mg of compound **1** and 2.2 equiv. of Na_2CO_3 (to **1**) were dissolved in 1.0 mL of PBS buffer (pH = 7.4), the gel would form being kept at 37 °C for 12 h. The gel could be imbibed to a syringe and then injected out from it. We observed the re-formation of a gel after 5 min.

2.2. Analysis of hydrolysis process during hydrogel formation

20.0 mg compound **1** and 2.2 equiv. of Na_2CO_3 were dissolved in 1.0 mL of PBS buffer (pH = 7.4). Tubes with 20 μL of the above solution were put at 37 °C. 200 μL of

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