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Invited review

Current research on hyaluronic acid-drug bioconjugates

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ABSTRACT

Hyaluronic acid (HA) is a mucopolysaccharide acid composed of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine. Based on numerous characteristics such as viscoelastic properties, water-binding ability, biocompatibility and non-immunogenicity, HA has been approved by FDA for biological and medical applications. In addition, multifarious receptors of HA like CD44, RHAMM and TSG6 are over-expressed on the surface of malignant cells, which play important roles in targeting ability. Bioconjugates linking drugs to HA could improve solubility, prolong half-life, provide active targeting capability and then increase the bioavailability of these coupled drugs by pro-drug strategy. Therefore, a large number of HA-drug bioconjugates have been studied. The purpose of this review was to summarize these HA-drug bioconjugates and further discuss synthetic methods and the relevant application in pharmaceuticals.

1. Introduction

Based on biocompatibility, biodegradability, non-immunogenicity, water-bonding property and receptors such as CD44, RHAMM, TSG6, HA has drawn lots of attention in pharmacy [1–6]. In addition, HA held many significant biological functions such as stabilizing and organizing extracellular matrix, regulating cell adhesion and motility [7–9]. Therefore, HA and its derivatives have been studied widely [10]. In the biopharmaceutics classification system, there is a kind of drugs suffering from low bioavailability because of the low solubility and low permeability. A pro-drug strategy of HA-drug conjugates could make full use of the superiorities of HA to make up for many deficiencies of these drugs. In the past few decades, investigators have devoted numerous efforts to develop HA-drug bioconjugates to enhance targeting ability, improve bioavailability and weaken adverse effects [11,12]. For example, HA-Exendin 4 and HA-Insulin bioconjugates were studied for the treatment of diabetics [13–19], which were prepared by peptide covalently combined with HA to prolong the short half-life, enhance stability and therapeutical effect [14,20–24]. Through vast trials and attempts, great achievements have been made.

The aim of this paper was to present an overview of synthesis and evaluation of HA-drug bioconjugates. The structural formulas and corresponding thumbnails of HA and all drugs were showed in Table 1 and structural formulas of linkers in HA-drugs bioconjugates were showed in Table 2. Detailed examples were illustrated and discussed as reference for future research and application.

2. HA-anticancer drug bioconjugates

2.1. HA-anticancer drug bioconjugates with linker

Owing to steric hindrance, HA and anticancer drugs could not be directly combined covalently. Therefore, the bioconjugates need linkers the process needs of synthesis, which are discussed as follows in details.

2.1.1. HA-paclitaxel bioconjugate

Paclitaxel (PTX), initially extracted from the bark of pacific yew, is a powerful anticancer drug [25,26]. However, many disadvantages such as poor solubility, toxic side effects and drug-resistance limited the application of PTX. A lot of investigations have been conducted to overcome these disadvantages [27]. Luo et al. prepared HA-PTX conjugate by the dihydrazide method [28] (Fig. 1A). PTX was combined to HA with anhydride and hydrazide as spacers. HA was activated by 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide (EDC) and reacted with adipic dihydrazide (ADH) to obtain HA-ADH. PTX was reacted with succinic anhydride (Suc) in the presence of pyridine for 3 days at room temperature to obtain the 2′-hemisuccinate PTX derivative (PTX-Suc) [29]. Then the PTX-Suc

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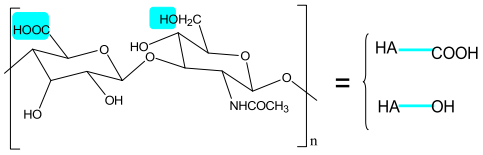
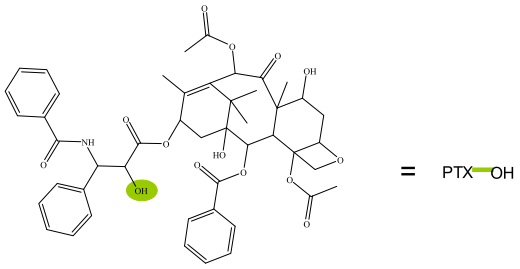
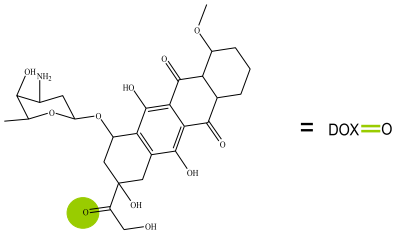
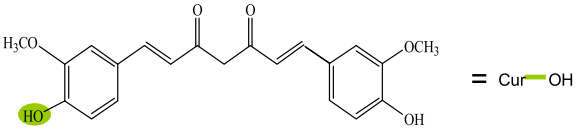
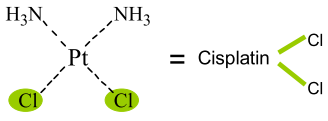
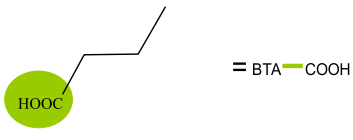
Table 1
Structural formulas and thumbnail of HA and drugs.

HA and Drugs	Structural formula and thumbnail	References
Hyaluronic acid(HA):		
Paclitaxel(PTX):		[28, 31, 32, 33]
Doxorubicin(DOX):		[39]
Curcumin(Cur):		[47]
Cisplatin:		[48]
Butyrate(BTA):		[56]