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# Tumor targeting strategies for chitosan-based nanoparticles

Xingzhen Zhang[a], Xiaoye Yang[a], Jianbo Ji[a], Anchang Liu (PhD) (Professor)[b,**], Guangxi Zhai (Ph.D) (Professor)[a,*]

[a] Department of Pharmaceutics, College of Pharmacy, Shandong University, Jinan 250012, China
[b] Department of Pharmacy, Qilu Hospital of Shandong University, Jinan 250012, China

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ABSTRACT

Currently, targeted nanoparticles (NPs) are rapidly being developed to overcome various bottlenecks of antitumor agents, such as poor solubility in aqueous solution, poor pharmacokinetics, a lack of selectivity and undesirable side effects in healthy tissues. In recent years, chitosan, a cationic polysaccharide, has been widely explored for the targeted delivery of antitumor agents due to its unique physicochemical and biological properties, such as biocompatibility, biodegradability, mucoadhesive feature, absorption enhancement and active functional groups for chemical modifications. This article reviews the recent developments in various target-specific nanoparticles based on chitosan and its derivatives, including passive, active and stimuli-sensitive targeting strategies. In addition, the target mechanisms and the key efficacy factors are illuminated.

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* Corresponding author at: Department of Pharmaceutics, College of Pharmacy, Shandong University, 44 Wenhua Xilu, Jinan 250012, China.
** Corresponding author.
*E-mail addresses:* acleu@126.com (A. Liu), professorgxzhai@126.com (G. Zhai).

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## 1. Introduction

Cancer is one of the major malignant diseases in the world. Common cancer treatments include chemotherapy, radiation, and surgery with chemotherapy. Among these treatments, surgery with chemotherapy has been the major treatment modality [1]. However, current chemotherapeutic agents are often limited by their undesirable properties, such as poor solubility, nonselective distribution and unwanted side effects after oral/intravenous administration, which may lead to cancer treatment failure [2]. An effective approach to solving this critical issue is the development of targeted nanoparticles to deliver these chemotherapeutic agents. Typically, nanoparticles offer many advantages such as small particle size, greater drug efficacy, lower toxicity, enhanced drug solubility and stability [3]. According to the enhanced permeability and retention (EPR) effect, nanoparticles can easily accumulate at the tumor site at high concentrations due to the pathophysiological differences between normal tissues and tumor tissues; this phenomenon is known as passive targeting [4]. In addition, ligand-receptor, antigen-antibody and other forms of molecular recognition by conjugation of targeting molecules onto nanoparticles to obtain targeted delivery to specific cells, tissues or organs are known as active targeting, which can maximize the drug therapeutic efficacy and reduce its systemic side effects [5,6]. More recently, researchers have shown interest in stimuli-responsive polymeric systems which have a phase transition in response to an external physical or chemical stimulus such as temperature, pH, or a specific ion [4]. In recent years, certain types of materials, such as dendrimers, lipids and surfactants, have been employed as tumor-targeted drug-delivery carriers for cancer therapy. Chitosan is a natural linear aminopolysaccharide derived from chitin, the second most abundant polysaccharide on earth after cellulose. Chitosan is composed of randomly distributed (1 → 4) linked D-glucosamine and *N*-acetyl-D-glucosamine units [7,8]. Compared to other polymeric nanoparticles, chitosan-based nanoparticles have excellent characteristics for tumor targeting: (1) the amino groups in chitosan are protonated at slightly acidic conditions, which allows chitosan-based nanoparticles to penetrate the cellular membrane and escape from endosomes [9]; (2) chitosan-based nanoparticles have the potential to modulate the pharmacokinetic and pharmacodynamic profiles of therapeutic agents due to their ability to inhibit P-glycoprotein, uptake by microfold cells; (3) chitosan is considered to have a direct effect on tight junctions and be able to bypass these junctions in epithelial cells, thus enhancing the paracellular permeability [10]; (4) chitosan allows specific chemical modifications to form a wide range of derivatives since it has primary amine groups and hydroxyl groups on its monomeric units. Chemically modified chitosan derivatives have broad developmental potential in the formulation of tumor-targeted drug-delivery carriers [11,12]. Therefore, the primary focus of this review is to discuss chitosan-based nanoparticles for different types of tumor-targeted drug delivery.

## 2. Chitosan-based derivatives

Chitosan is a linear polyamine containing three types of reactive functional groups, an amino group and primary and secondary hydroxyl groups at the C-2, C-3 and C-6 positions in its structure, respectively; these groups are readily available for modification or grafting. Moreover, its cationic nature allows for ionic cross-linking with multivalent anions [13,14]. Chemical modification makes it possible to improve the properties of native chitosan and offers broad developmental opportunities for using chitosan for pharmaceutical and biomedical applications [15]. Numerous chitosan-based derivatives have been reported, as shown in Table 1.

### 2.1. Chitosan derivatives

O-carboxymethyl chitosan (OCMC) is a type of chitosan derivative with a $CH_2COOH$ modification at the C6 position. OCMC has many advantages, such as enhanced solubility in aqueous solutions and improved stability [21]. In addition, the carboxyl group on OCMC is available and has a high capacity for binding to $Ca^{2+}$. This binding ability could deprive the divalent ions from the extracellular matrix and increase the paracellular permeability of the epithelium [22]. Sahu et al. reported that pH-sensitive carboxymethyl chitosan (CMC) nanoparticles modified with folic acid were effective targeted drug delivery vehicles with an average size less than 200 nm. Due to their folate-mediated targeting, the nanoparticles could considerably enhance the cellular uptake and thus facilitate apoptosis of cancer cells (HeLa, B16F1). For intracellular uptake evaluation, flow cytometry was used to study the behavior of CMC-folate-FITC nanoparticles for targeting to B16F1 and HeLa cancer cells along with NIH3T3 and L929 noncancerous cells. The mean values of the fluorescence intensities for HeLa and B16F1 cells were 228.62 and 103.93, respectively, and fluorescence intensities for NIH3T3 and L929 cells were 37.43 and 85.4, respectively, indicating a significantly higher uptake of nanoparticles by the cancer cells compared with normal cells. Moreover, the nanoparticles demonstrated pH sensitivity, as the release of DOX from CMC-folate nanoparticles was 62% at pH 5 and 51% at pH 7.4 after 100 h [16].

Glycol chitosan (GC) is a chitosan derivative with ethylene glycol groups on its backbone, and its water solubility is highly enhanced by these glycol groups. Koo. et al. developed hydrotropic oligomer-conjugated glycol chitosan nanoparticles (HO-CNPs) for tumor-targeted delivery of paclitaxel (PTX). The PTX-encapsulated HO-CNPs (PTX-HO-CNPs) had an average size of 343 nm and a high drug-loading amount of up to 24.2 wt%. PTX-HO-CNPs showed fast cellular uptake through clathrin-mediated endocytosis, caveolae, and macropinocytosis in MDA-MB231 human breast cancer cells. *In vivo*, although PTX-HO-CNPs showed similar tumor accumulation with Abraxane® treatment, it had a two-fold larger amount of PTX compared with the Abraxane® due to its high load efficiency [17].

Wang et al. investigated an efficient and targeted system for delivery of antisense oligodeoxynucleotides (asODNs) using folic acid (FA)-conjugated hydroxypropyl-chitosan (HPCS) [23]. The diameter of the nanoparticles was 181 nm. The results of an *in vitro* release study showed that 40% of the asODNs were released from the nanoparticles in the first 24 h. However, only another 15% were released between 24 and 48 h, which might be due to the longer diffusion path of asODNs inside the nanoparticles. In the reversion test of multidrug resistance (MDR), the cytotoxicity assay in drug-

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