Chapter

Targeted Nano-Drug Delivery System to Colon Cancer

Eskandar Moghimipour and Somayeh Handali

Abstract

Cancer has been considered as the most cause of death in world. Employing of nanocarriers as drug delivery systems provide a platform for delivering drugs with increasing the anti-cancer efficacy, enhancing bioavailability of drugs, reducing side effects, enhancing the circulation half-life of drugs, improving the distribution of drugs and overcoming drug resistance. A number of nanocarriers have been studied as drug delivery systems for improving the treatment of cancer including liposomes, micelle, polymeric nanoparticles, carbon nanotubes, dendrimers, solid lipid nanoparticle (SLN) and nanostructure lipid carrier (NLC). In order to enhance recognition and internalization of nanocarriers by the target tissues, their surfaces can be modified with targeting ligands such as integrins, transferrin, folic acid, polysaccharides and antibodies. In this chapter, we are going to introduce the targeted nanocarriers for improving the cytotoxic action of drugs with further attempt of decreasing dose to achieve higher anticancer activity. Targeted nanocarriers would provide a promising therapeutic approach for cancer.

Keywords: Colon cancer, Nanoparticles, Drug delivery

1. Introduction

Colon cancer is one of the most commonly causing death in the world [1]. The conventional chemotherapy for colon cancer has a poor efficacy due to side effects on normal cells [2, 3]. Moreover, development of *multidrug resistance* (*MDR*) remains a major obstacle in the cancer treatment [4]. Using of nanocarriers as drug delivery systems provide a platform for delivering of drugs with increasing the anti-cancer efficacy, reducing side effects, improving therapeutic index, increasing the solubility of drugs, increasing bioavailability of drugs, enhancing the circulation half-life of drugs, improving the distribution of drugs and overcoming drug resistance [5, 6].

A number of nanocarriers have been employed as drug delivery systems for improving cancer treatment including dendrimer [7], chitosan [8], liposome [4], polymeric NPs [9], micelle [10] and exosomes [11]. Decorated nanocarriers with targeted ligands can identify receptors on cell surface which lead to enhance cellular uptake, reduce adverse effects and provide effective release of drugs [12, 13].

2. Nanocarries for colon cancer drug delivery

Sodium alginate, as natural polysaccharide is widely considered as a polymer for drug delivery due to hydrophilic, biodegradability, biocompatibility and

negatively charged. Stable micelles of sodium alginate-curcumin bioconjugate were developed for anti-cancer applications. Sodium alginate-curcumin bioconjugate rapidly internalized in colon cancer cells; however, normal cells were less sensitive to this bioconjugate. Moreover, these micelles did not induce hemolysis and red cells aggregation [10].

Dendrimers are widely considered as nanocarrier for drug delivery due to biocompatibility, high drug loading and high surface functionality [7]. PAMAM G5 dendrimers encapsulated with curcumin and gold NPs (AuNPs) and decorated with MUC-1 aptamer were developed for targeted delivery to the colon cancer. AuNPs improve the contrast and resolution in the computed tomography (CT). MUC-1 receptors are overexpressed in the colorectal cancer; therefore, they can be considered as target for active targeting drug delivery. Targeted PAMAM dendrimers exhibited higher cellular cytotoxicity than non-targeted nanocarriers due to the higher affinity between MUC1 aptamer and MUC-1 receptor in cancer cells which increases the internalization of nanocarriers through receptor-mediated endocytosis. *In vivo* studies also illustrated the capability of targeted dendrimer as an effective theranostic system for colon cancer [13].

Employing of pH-controlled drug delivery systems lead to release of drug under acidic condition and not under neutral condition. CuS@Cu2S@Au nanoparticles (NPs), as a pH-sensitive carrier developed for delivery of doxorubicin (DOX) to colon cancer cells. The drug loaded NPs exhibited pH sensitive release and higher toxicity than free drug on cancer cells. Furthermore, these NPs showed good biocompatibility which make them as promising carrier for drug delivery [5].

Chitosan (CS) as biocompatible polymer is mostly considered as drug delivery system due to *low* toxicity, *low immunogenicity*, *bioadhesion* and *biodegradability* [8]. In addition, CS increases the permeability of drugs by regulating the tightness between cells [2]. CS NPs were prepared for oral co-delivery of 5-Aminolevulinic acid (5-ALA) and photothermal agent (IR780). Results showed that co-delivery system increased photodynamic effects against colon cancer cells *via* enhancing oxidative stress, ROS, superoxide and $^1O_2$ production [14].

Luteolin is found in numerous plants that is showed remarkable anti-cancer activity against skin, breast, liver, prostate and colon cancer. However, its clinical application is limited due to poor solubility and low bioavailability. A liposomal formulation was designed for improving the anti-tumor activity of luteolin. Liposomal luteolin significantly displayed anti-cancer activity against colon cancer cells than free luteolin *in vitro* and *in vivo*. These findings indicated that liposome formulation improved solubility and bioavailability of luteolin [15]. Mannose receptors are overexpressed in the drug resistant human colon tumor cell lines. Dihydroartemisinin (DHA, a derivative of artemisinin) and DOX were co-loaded into mannosylated liposomes for targeted delivery to colon cancer cells. These targeted liposomes increased the accumulation of both drugs in cancer cells which led to inhibit the growth of cancer cells through enhancing apoptosis, low expression of Bcl-xl and induction of autophagy [4].

5-Fluorouracil (5FU) has been commonly used for treatment of colon cancer. However, its medical application is restricted due to *multidrug resistance*, short half-life, side effects and low therapeutic index [16, 17]. Folic acid-decorated liposomal drug delivery system was designed for tumor targeting of 5FU. Targeted liposomes displayed higher cellular uptake and more activated apoptotic pathway than free drug on cancer cells. Results of hemolysis assay indicated the blood biocompatibility of the liposomes. Furthermore, folate targeted liposomes exhibited better tumor inhibition than free drug [18, 19]. Transferrin targeted liposomal 5FU also triggered apoptosis through mitochondria signaling pathway in cancer cells [20].

Cell differentiation 44 (CD44) is also frequently overexpressed on colon cancer cells. CD44 is the major receptor of hyaluronic acid (HA) in cancer cells. A smart

micelle formulation was prepared using tocopherol succinate (TOS) conjugated HA by redox-responsive disulfide bond as a linker. According to the results, the micelle could specifically attach to CD44 receptors overexpressed tumor cells and responded selectively to high level of glutathione (GSH) in cells which led to inducing disulfide bond breakage and the release of paclitaxel (PTX) and triggered apoptosis in cancer cells [21].

A biocompatible pH-sensitive copolymer methoxy poly (ethylene glycol)-b-poly[(hydroxypropyl methacrylamide)-g-α-tocopheryl succinate-g-histidine)] (PTH) was synthesized for co-delivery of DOX and α-TOS. Results of *in vivo* biodistribution showed that micelles considerably accumulated in the cancer tissues. Moreover, these formulations exhibited higher cytotoxicity on cancer cells than normal cells [22].

PLGA, a synthetic copolymer is widely employed as nanocarrier for drug delivery system due to biodegradable, biocompatible and non-immunogenic [23]. DOTAP-PLGA hybrid NPs were prepared for delivery of 17-allylaminogeldanamycin (17AAG) as a HSP90 inhibitor and NPs were decorated with HA. Findings showed that internalization of HA-NPs in colon cancer cells was through CD44 receptor mediated endocytosis. HA-NPs-17AAG induced apoptosis more than free 17AAG in cancer cells. Additionally, HA-NPs-17AAG significantly inhibited tumor growth than free 17AAG in mice [12]. Poly (3-hydroxybutyrate-co-3-hydroxyvalerate acid) (PHBV)/PLGA NPs were developed for co-delivery of 5FU and oxaliplatin for colon cancer treatment. Co-loaded NPs showed significantly higher cytotoxicity and anti-tumor efficiency compared to free drugs combination, indicating that PHBV/PLGA NPs can be employed as a platform for co-delivery of 5FU and oxaliplatin [23].

Nanogels are nanosized particles that are formed by chemically or physically crosslinked polymer networks [24]. Folic acid functionalized amylopectin-albumin core-shell nanogels were designed for improving colon cancer cell targeted delivery of curcumin. The curcumin loaded in nanogels exhibited stability against physiological degradation and efficiently triggered apoptosis than free curcumin in HT29 cells.

Exosomes are natural membrane vesicles that are secreted into the extracellular environment and can be exploited as drug delivery. Exosomes contain bioactive molecules such as lipids, DNA, mRNAs and proteins [11]. Engineered exosomes were designed for co-delivery of 5FU and miR-21i (miR-21 inhibitor oligonucleotide) to colon cancer cells. The engineered exosome efficiently facilitated cellular uptake of drugs and significantly inhibited miR-21 expression in 5FU resistant colon cell lines and increased apoptosis. Moreover, systematic administration of 5FU and miR-21i encapsulated exosomes significantly showed anti-cancer effect in mice [16].

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