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Promising Application of Nanotechnology in Anticancer Drug Delivery

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Cancer is a major public health problem in the world. Despite cancer patients have benefited from the existed cancer therapy protocols, cancer therapy still remains great challenges [1]. Because of the great potential application of nanotechnology in cancer, cancer nanotechnology is emerging as a new field of interdisciplinary research [2]. The use of nanoparticles for drug delivery is likely one of the most clinically important applications of cancer nanotechnology [3].

One essential factor in the drug development equation is drug solubility. Many drug candidates fail to be developed because of their poor water solubility, which makes their formulation difficult or even impossible. For example, camptothecin is widely recognized as an efficient anticancer agent *in vitro*, but its clinical application is actually limited by its bad solubility [4]. Nanotechnology provides a novel method to overcome the poor water solubility of hydrophobic drugs. Encapsulation of hydrophobic drugs into nanoparticles (<200 nm) can render the drug completely dispersible in water, making the drug intravenously injectable. After the drug loaded nanoparticles are administrated, the drug can be released from nanoparticles to play its role [5]. Traditional paclitaxel formulation contains Cremophor EL. Samyang Corporation (Korea) uses methoxy-PEG-poly (D, L-lactide) to encapsulate paclitaxel, successfully creating a Cremophor EL-free paclitaxel formulation: Genexol-PM®, which has been marketed in Korea. ABRAXANE® (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is another marketed Cremophor EL-free formulation of paclitaxel [6].

Most current anticancer drugs can not greatly differentiate between cancerous and normal cells, leading to systemic toxicity and adverse effects. Consequently, anticancer drugs always have a limited maximal allowable dose. In addition, rapid elimination and widespread distribution into non targeted organs and tissues require the application of a drug in large dosage, which is not economical and is often complicated owing to nonspecific toxicity. Taking advantage of the inherent size of nanoparticles and the unique properties of tumor vasculature the tumor microenvironment, anticancer drug can be passively targeted to cancers to enhance anticancer efficacy and reduce systemic toxicity [7]. Angiogenic blood vessels in tumor tissues, unlike those in normal tissue, have gaps (200~1200 nm) between adjacent endothelial cells. This defective vascular architecture, coupled with poor lymphatic drainage, can induce the enhanced permeability and retention (EFR) effect, which allows nanoparticles delivered drugs to extravasate through these gaps into extravascular spaces and accumulate inside tumor tissues [8]. Meanwhile, tumors always have an acidic microenvironment. Thus, pH-sensitive nanoparticles can be used to slowly release drugs at physiological condition (pH=7.4), but fast release at acid condition (pH=5~5.5), leading to the selective release of anticancer drug in tumor site [9]. Otherwise, cancer cells overexpress and release some enzymes that are crucial to tumor migration, invasion, and metastasis; this allows drug-loaded nanoparticles with tumor-associated molecules-sensitive release behavior can be used in tumor-specific drug delivery [10]. Also, it is found that nanoparticles can reduce extravasation of drug from the normal blood vessel but not angiogenic blood vessels in tumor, contributing to reduce the side effects [11]. Doxorubicin is one of the most widely prescribed and effective cytotoxic drugs used in oncology. However, doxorubicin is inadequate as a chemotherapeutic agent, because it is known to cause short- and long-term cardiac toxicity. Recent studies indicated that encapsulation of doxorubicin in nanoparticles can provide a platform technology for improving the anticancer efficiency as well as reducing the side effects [12]. And liposomal doxorubicin is already marketed for cancer treatment [6]. Furthermore, nanoparticles can be designed to actively target cancer, which is usually achieved by conjugating to the nanoparticle a targeting component that provides preferential accumulation of nanoparticles in the tumor bearing organ, tumor itself, individual cancer cells, or intracellular organelles inside cancer cells [7]. This approach is always based on specific interactions, such as lectin-carbohydrate, ligand-receptor, and antibody-antigen. Several targeted polymeric nanoparticles are undergoing clinical studies [6].

Gene therapy provides a novel method for cancer therapy and holds promising clinical application. Up to now, almost 2000 gene therapy protocols are studied in clinical, of which cancer gene therapy takes 64% [13]. Some gene therapy drugs are already marketed in China Europe or Russia. Lacking of safe and efficient gene delivery system is a critical obstacle to gene therapy [14]. Viral gene vector always has high transfection efficiency, but its potential safety issue should be concerned. After several failures of clinical gene therapy were caused by the severe side effects of viral vectors, the safety becomes the first issue to be considered when a gene delivery system is developed for clinical gene therapy. And non-viral gene carriers were paid extensive attentions, because of the low immunogenicity, relative safety, ability to deliver larger DNA molecules, and easy to produce and scale up [15]. Recently, many attempts have been paid to prepare novel non-viral gene delivery system by nanotechnology. For example, polyethyleneimine (PEI) is one of the most efficient non viral gene transfection agents; but PEI is not biodegradable and has a shortcoming, i.e., the increase in transfection efficiency is accompanied by the increase in cytotoxicity, and both efficiency and cytotoxicity increase as its chain length increases. Recent studies demonstrate that conjugation of low molecular weight PEI into nanoparticles by degradable linkers can create novel PEI derives with high transfection efficiency and low cytotoxicity, contributing to improving the potential of PEI in cancer gene therapy [16].

Immunotherapy is another method for cancer therapy. The

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development of human therapeutic cancer vaccines has come a long way since the discovery of MHC-restricted tumour antigens in the 1980s. The new generation antigens, especially those based on recombinant proteins and DNA, are likely to be poorly immunogenic. Meanwhile, efficient cellular immune responses are desired for cancer immunotherapy [17]. So, vaccine delivery system became necessary for inducing effective cancer immunotherapy. Alum (aluminium salts) is a potent adjuvant that has been licensed for human use. But it is not efficient in enhancing the cellular immune response against antigen. Using nanoparticles to deliver antigen can contribute to prolong the half-life of antigen, target antigen presentation cells (APCs) and induce cellular immune response [18]. Furthermore, vaccine delivery system based on nanoparticles had promising application in single-dose vaccine, needle-free vaccine, transdermal vaccine, oral vaccine, and inhaled vaccine. And developing novel vaccine delivery system is a current focus of cancer immunotherapy research.

Summarily, application of nanotechnology in anticancer drug delivery can contribute to improve or enable treatments of cancer. Rationally designed nanoparticles have promising clinical application in cancer chemotherapy, cancer gene therapy and cancer immunotherapy. More clinical researches of cancer therapy with nano-drug are desired to deeply understand the critical issues of applying nanotechnology in cancer. Effective collaborations between scientists from different fields (such as materials, nanotechnology, chemistry, physics, pharmacology/pharmaceutics, oncology, medicine, etc) may be very important to push more nano-drugs to market, with the goal of benefiting cancer patients.

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