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Mini-review

Nanoscale drug delivery for targeted chemotherapy

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ABSTRACT

Despite significant improvements in diagnostic methods and innovations in therapies for specific cancers, effective treatments for neoplastic diseases still represent major challenges. Nanotechnology as an emerging technology has been widely used in many fields and also provides a new opportunity for the targeted delivery of cancer drugs. Nanoscale delivery of chemotherapy drugs to the tumor site is highly desirable. Recent studies have shown that nanoscale drug delivery systems not only have the ability to destroy cancer cells but may also be carriers for chemotherapy drugs. Some studies have demonstrated that delivery of chemotherapy via nanoscale carriers has greater therapeutic benefit than either treatment modality alone. In this review, novel approaches to nanoscale delivery of chemotherapy are described and recent progress in this field is discussed.

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Introduction

Despite significant advances in the diagnosis and treatment of cancer, it remains the second most common cause of mortality [1], owing to the limited efficacy of chemotherapeutic agents and multidrug resistance (MDR) [2]. These limitations are frequently due to the development of genetic mechanisms within tumor cells that override apoptosis despite the damage to the tumor cell DNA caused by chemotherapy. Additionally, surviving patients suffer various serious side effects of the available anti-neoplastic medicines. Research and development has traditionally focused on developing a single curative drug for each type of cancer, but combination therapy has emerged as the most promising strategy for improving survival. Therefore, much effort has been directed toward finding alternative pathways that complement the therapeutic induction of apoptosis and overcome MDR.

The success of nanomedicine as a new strategy for targeted drug delivery has prompted interest in developing novel approaches within basic and clinical oncology. With the development of new nanobiological technologies, nanotechnology has been applied in molecular imaging, drug delivery, and therapy, and thus, provides new research opportunities for tumor-targeted drug delivery [3]. Nanoscale drug delivery systems for tumor targeting are based on the delivery of anti-tumor drugs within nanocarriers capable of targeting tumor tissues by taking advantage of the physiological and pathological characteristics of tumors [4]. One study reported that a nanoscale chemotherapy delivery system for the treatment of malignant tumors can enhance the sensitivity of tumor cells to chemotherapeutic drugs while also limiting the invasion and metastasis of the tumor [2]. Moreover, nanoscale delivery of chemotherapy shows promise for reducing the side effects of therapy by targeting the action of drugs on cancer cells. In recent years, liposomes, nanoparticles, and polymeric micelles have been frequently studies for use as nanocarriers, and each type of nanocarrier has its own distinctive advantages over other nanomaterials. For improved cancer treatment, it is important for the nanoscale drug delivery systems to selectively and specifically target tumors. The mechanisms of nanocarriers' anti-tumor effects can involve targeting cancer stem cells to overcome MDR and prevent recurrence, preventing the cross talk between cancer cells and their microenvironment, and modifying the immune response to improve the treatment of MDR cancers.

In this review, we provide an overview of novel anti-tumor nanoscale drug delivery systems and discuss their characteristics, recent progress, possible mechanisms of action, and perspectives.

Characteristics of different nanoscale chemotherapy delivery systems

Nanotechnology is an emerging field that has shown great promise in the development of novel diagnostic and therapeutic agents for a variety of diseases, including cancers [5]. In the field

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of cancer research, one advantage of nanocarriers for chemotherapy delivery is the enhanced permeability and retention (EPR) effect that enables nanocarriers to accumulate in tumors at much higher concentrations than in normal tissue [6]. As the vasculature in tumors is known to be leaky and the tumor lymphatic system is also deficient, nanocarriers can preferentially accumulate in the tumor site via the EPR effect [7]. Moreover, nanocarriers can be designed with optimal size and surface characteristics to increase the time in circulation and biodistribution [6]. To achieve enhanced therapeutic efficacy and reduced side effects, nanoscale drug delivery carriers have been studied due to both their enhanced tumor accumulation and controllable drug release features. Examples include liposomes, nanoparticles, polymeric micelles, and others, and each type of nanocarrier has unique characteristics.

Liposomes composed of phospholipids and cholesterol have a bilayer structure similar to biological membranes, which can range in diameter from 25 to 1000 nm [8]. The liposome structure contains hydrophilic groups and hydrophobic groups, because phospholipid is an amphoteric substance [9]. The prominent characteristics of liposomes are their biocompatibility and cellular affinity [10]. In addition, liposomes can be biodegradable in vivo and have no immunogenicity [11], due to their similarity to the biological cell membrane structure. Liposome uptake in the human body can change the in vivo distribution of the encapsulated drugs, primarily in the liver, spleen, lung, and lymph system, etc. Therefore, liposomes offer a certain degree of organ targeting. Liposomes also offer the advantage of being easily modifiable [8]. If the liposome membrane is modified, such as by changing the charge on the membrane surface, the cycle time of liposomes in vivo can be prolonged, and the target tissue also can be changed. In addition, liposomes can be used for sustained release of encapsulated drugs and can reduce the toxicity of chemotherapy drugs to normal tissues. Liposomes can improve the pharmacological properties of a drug by altering the pharmacokinetics and biodistribution, protecting the drug against degradation and facilitating targeted delivery of the drug [6,12]. The selectivity and efficacy of chemotherapy can be further improved through active targeting achieved by equipping the liposomes with ligands. For binding to cancer cells, liposomes must extravasate from circulation and penetrate the tumor tissue. Due to high interstitial pressure, extravasation is often inefficient [13]. A variety of novel targeted liposomes have been extensively developed in recent years, such as proliposomes, immunoliposomes, long-circulating liposomes, temperature-sensitive liposomes, and PH-sensitive liposomes [14]. Considering long-circulating liposomes as an example, liposomes can be modified by PEG to increase their flexibility and hydrophilicity, prolong their time in circulation, and target tissues or organs other than the liver and spleen via phagocytosis from the mononuclear phagocyte system, which reduces the interaction between the liposome membrane and plasma proteins [15]. Although liposomes have been used as potential nanocarriers with unique advantages, their application is limited due to inherent problems such as low drug encapsulation efficiency, rapid leakage of water-soluble drugs in the presence of blood components, and poor storage stability.

In contrast, nanoparticles offer some specific advantages over liposomes. Nanoparticles are particulate dispersions or solid particles with a size in the range of 10–1000 nm [16]. Nanoparticle is a collective name for nanospheres and nanocapsules [17] made from biocompatible and biodegradable materials such as polymers, either natural (e.g., gelatin, albumin) or synthetic (e.g., polylactides, polyalkylcyanoacrylates), or solid lipids [18]. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, whereas nanospheres are matrix systems in which the drug is physically and uniformly dispersed. The drug is adsorbed, dissolved, or dispersed throughout the matrix in nanospheres and is confined to an aqueous or oily core surrounded by a shell-like wall in nanocapsules [19]. Alternatively, the drug can be covalently attached to the surface or into the matrix, and the drug loaded in nanoparticles is usually released from the matrix by diffusion, swelling, erosion, or degradation in vivo. The following are among the advantages of nanoparticles as drug carriers: high stability (i.e., long shelf life), high carrier capacity (i.e., many drug molecules can be incorporated in the particle matrix), and feasibility of incorporation of both hydrophilic and hydrophobic substances [18]. The particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration. Nanoparticles offer controlled and sustained release of the drug during its transportation and at the site of localization, altering the organ distribution of the drug and subsequent clearance of the drug to achieve increased drug therapeutic efficacy and a reduction in side effects. Drug loading is relatively high, and drugs can be incorporated into the systems without any chemical reaction.

In general, drug delivery systems have been investigated for many years, and among them, polymer micelles as a new type of nanocarrier with an appropriate size range (10–100 nm) offer a promising alternative. Polymer micelles as drug delivery systems have been reported to combat MDR through absolute targeting using various approaches such as passive targeting, folate-mediated drug delivery systems, and pH-sensitive and thermosensitive drug delivery systems [20]. Because of the particle size range of polymer micelles and their hydrophilic outer shell and hydrophobic core, polymer micelles are suitable for carrying different drugs, can help the drug avoid excretion via the kidney while also avoiding phagocytosis of the endothelial reticular system, and can prolong the circulation time of the drug [21]. Polymeric micelles are thermodynamically stable, and the hydrophilic shell enhances their stable dispersion in aqueous solution via a steric stabilization effect, which supports its long-term blood duration following intravenous injection [22,23]. The stability of polymer micelles, which affects the stability of encapsulation of guest molecules, may be a crucial condition for some controlled delivery applications. Polymeric micelles combined with a tumor targeting agent applied in chemotherapy can effectively improve the water solubility of chemotherapeutic drugs, increase the utilization rate and anti-tumor activity of chemotherapy drug, reduce the toxic side effect on normal cells, solve the problem of MDR to greatly improve the effect of tumor chemotherapy, and promote the development and progress of tumor chemotherapy [20]. Polymer micelles as drug carriers also have other advantages: the EPR effect, good biocompatibility, and low side-effects. However, polymeric micelles may be associated with drug leakage and drug burst release.

Although many different nanocarriers share similar characteristics, individual carriers have unique characteristics, such that different carriers can complement each other. In follows then that different nanocarriers are applied in unique areas. Table 1 outlines the characteristics of various types of nanocarriers.

Current status of nanoscale delivery of chemotherapy in the treatment of cancer: targeted chemotherapy in multiple cancers

Cancers cause millions of deaths around the world every year [32], and chemotherapy remains the primary modality of cancer treatment. However, the specificity of chemotherapy drugs and MDR can easily lead to tumor recurrence. Therefore, it is of great significance to reverse the MDR of tumor cells and enhance their sensitivity to chemotherapeutic drugs [2]. Chemotherapy resistance remains a major obstacle to successful clinical cancer therapy, mainly due to the low level of accumulation and low sensitivity of drugs and the absence of effective clinical strategies. An additional obstacle is the inability of chemotherapy drugs to selectively target

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