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Research review paper

Nanotechnology-based intelligent drug design for cancer metastasis treatment

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ABSTRACT

Traditional chemotherapy used today at clinics is mainly inherited from the thinking and designs made four decades ago when the Cancer War was declared. The potency of those chemotherapy drugs on in-vitro cancer cells is clearly demonstrated at even nanomolar levels. However, due to their non-specific effects in the body on normal tissues, these drugs cause toxicity, deteriorate patient's life quality, weaken the host immunosurveillance system, and result in an irreversible damage to human's own recovery power. Owing to their unique physical and biological properties, nanotechnology-based chemotherapies seem to have an ability to specifically and safely reach tumor foci with enhanced efficacy and low toxicity. Herein, we comprehensively examine the current nanotechnology-based pharmaceutical platforms and strategies for intelligent design of new nanomedicines based on targeted drug delivery system (TDDS) for cancer metastasis treatment, analyze the pros and cons of nanomedicines versus traditional chemotherapy, and evaluate the importance that nanomaterials can bring in to significantly improve cancer metastasis treatment.

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1. Introduction

Cancer remains a leading cause of death worldwide (Ferlay et al., 2010). Although years of intense biomedical research and billions of dollars in spending have increased our understanding of the underlying mechanisms of tumorigenesis and biology of cancer, cancer mortality surprisingly reached to the highest point as the top killer in the US population younger than 85 years old (Jemal et al., 2010). Among them, cancer metastasis attributes to approximately 90% of cancer-related deaths (Veiseh et al., 2011). Although immunotherapy, thermal therapy, phototherapy (Jia and Jia, 2012; Shao et al., 2013) and gene therapy are available as cancer treatment modalities, surgery, radiation, and/or

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chemotherapy continue to be the therapeutic options for most cancers over decades, each with its own limitations. Surgery and radiation therapy could be effective for the primary tumor, however, they may not be a good treatment choice for metastases. Chemotherapy with cytotoxic agents is commonly used for the whole-body treatment of recurrent disease. But the conventional anticancer drugs generally result in serious side effects in clinic (Sinha et al., 2006; Stortecky and Suter, 2010; Tsuruo et al., 2003). The side effects are associated with the formulation due to poor water solubility of the drug, non-specific distribution, severe toxicity to normal cells, inadequate drug concentrations at tumors or cancerous cells, and the development of multidrug resistance. Therefore, researchers are continuously seeking for improved anti-cancer therapies that can selectively target tumor cells with minimal side effects on normal tissues (Wang et al., 2008).

Nanotechnology is the understanding of materials in the nano (10^{-9}) size range, and involves imaging, measuring, modeling, and manipulating materials within that framework. Since its advent, nanotechnology has revolutionized a wide range of medical products, generic tools and biotechnology equipment. Nanomedicine focuses on application of nanotechnology in medicine for diagnosis, prevention, detection, and treatment of the disease. In particular, it has been used to design and development of targeted drug delivery system (TDDS) which could safely deliver therapeutic drugs to injury sites or specific cells. For formulations intended for i.v. administration, effective TDDSs could retain therapeutic drug in the vehicle, evade the reticuloendothelial system (RES) uptake, target to intended sites of injury, and release drug at the intended sites with required drug concentration (Mills and Needham, 1999). In the field of oncology, TDDS offers many potential benefits such as (1) avoiding the side effects of the clinical formulation for improving solubility, (2) protecting the entrapped therapeutic drug from degradation, (3) modifying pharmacokinetic and tissue distribution profile to increase drug distribution in tumor, (4) reducing toxicity to normal cells, and (5) increasing cellular uptake and internalization in cancer cells. In the past 20 years, many nanomedicines have been in preclinical development and some of them have been approved for use in clinic including for cancer therapy (Davis et al., 2008; Jain and Stylianopoulos, 2010; Peer et al., 2007). Besides used as drug delivery systems (DDSs) for cancer therapy, nanoparticles loaded with imaging agents were also found useful in imaging techniques applied for tumor diagnosis. Here we will focus on TDDS designed for i.v. administration and for delivering anticancer drugs including chemotherapeutic drugs and therapeutic genes.

In this review, we first outline the different types of nanoparticle platforms currently being established for cancer treatment. We then present various strategies that have been employed in designing new effective TDDSs.

2. Current established nanoparticle platforms as drug delivery systems for cancer therapy

There are diverse types of nanocarriers that have been synthesized for drug delivery including dendrimers, liposomes, solid lipid nanoparticles, polymersomes, polymer-drug conjugates, polymeric nanoparticles, peptide nanoparticles, micelles, nanoemulsions, nanospheres, nanoshells, carbon nanotubes, and gold nanoparticles, etc. (Fig. 1). In all these types, drugs can be entrapped inside, dissolved in the matrix, covalently linked to the backbone, or absorbed on the surface. From the aspect of the property, these nanocarriers could be divided into organic, inorganic, and organic/inorganic hybrid nanoparticles. From the perspective of formulation type, they could be divided into liposomes, micelles, emulsions, nanoparticles, etc (Jia, 2005). Ljubimova and Holler also proposed the term 'nanopolymer' meaning a single polymer molecule in the nanoscale range, to distinguish with 'nano-polymer composites' such as micelles and other self-assembled or aggregated forms in the point of whether they could dissociate in solutions (Ljubimova and Holler, 2012). Here, we will categorize these current established nanoparticle platforms based on the difference in composition including lipid-based nanomedicine, polymer-based nanomedicine, peptide-based nanomedicine and inorganic nanomedicine for treating cancer. Some examples of nanomedicines that are approved for commercial use or still in clinical trials are listed in Table 1.

2.1. Lipid-based nanoparticle platforms

Lipid-based nanoparticles have attracted great attention as DDS due to their attractive biological properties such as good biocompatibility, biodegradability, low immunogenicity, and the ability to deliver hydrophilic and hydrophobic drugs. Liposomes are the most widely used and studied examples (Jia et al., 2002), with bilayer membrane structures composed of phospholipids for stabilizing drugs, directing their cargo toward specific sites, and for overcoming barriers to cellular uptake. Their aqueous reservoir and the hydrophobic membrane allow them to encapsulate either hydrophilic or hydrophobic agents. The important milestone that led to the development of clinically suitable liposome formulations could be the inclusion of PEGylated lipids in the liposomes to protect liposomes from destruction by the RES, thus to increase circulation time and increase drug accumulation in the tumors. It is worthy to mention that Doxil®/caelyx, a PEGylated liposome formulation of the anticancer drug doxorubicin (DOX), was the first formulation approved for application in the clinic (Barenholz, 2012). With the aim to site-specific delivery of cancer drugs to the cancerous tissues, the surface of liposomes can be modified with ligands or antibodies targeting those receptors overexpressed on cancer cell membranes (Gabizon et al., 2006). For tumor site-specific triggering drug release, liposomes were designed with responsive to changes in light (Leung and Romanowski, 2012), temperature (Park et al., 2013), acid (Mamasheva et al., 2011) or enzymes (Andresen et al., 2005). Though the work on modification of liposomes has achieved great progress, the application of liposomes in the clinic still poses several challenges including rapid clearance from the bloodstream, instability of the carrier, high production cost, and fast oxidation of some phospholipids.

Solid lipid nanoparticles (SLN) is an alternative to liposomes, the matrix of which comprises of solid lipids. They exhibit major advantages such as less cytotoxicity than polymeric counterparts; stable formulations, excellent reproducibility, avoidance degradation of incorporated, controlled drug release, and potential application in intravenous, oral, dermal or topical routes (Uner and Yener, 2007). However, some limitations still exist such as undesired particle growth by agglomeration or coagulation, ineffective drug loading capacity, rapid drug expulsion during storage due to lipid crystallization and high water contents of the dispersions. Thus, modified SLN, so-called nanostructured lipid carriers (NLC) were developed to overcome these limitations and combine the advantages associated with SLN. In contrast to SLN which are made from solid lipids core containing triglycerides, glyceride mixtures, or waxes, NLC were composed of liquid lipid and solid lipid (preferably in a ratio of 30:70 up to 0.1:99.9) to form a nanosized solid particle matrix. The imperfect crystal or amorphous structure assures them to have enhanced drug loading and less drug expulsion during storage (Iqbal et al., 2012). Till now, SLN and NLC as colloidal drug carriers have been successfully multi-functionalized to transport drugs to the targeted cancer cells and achieve efficient drug release in a controlled manner, which confirm their promising application in cancer therapy.

2.2. Polymer-based nanoparticle platforms

Polymer-based nanoparticle platforms show enormous potential for treating disease or repairing damaged tissues especially for cancer treatment, which relies on their remarkable properties including small size, excellent biocompatibility and biodegradability, prolonged circulation time in the bloodstream, enhanced drug loading capacity, and easy chemical modification or surface functionalization. The last two characters are the utmost important criteria for their clinical use. Generally