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Nanomedicine therapeutic approaches to overcome cancer drug resistance☆,☆☆

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ABSTRACT

Nanomedicine is an emerging form of therapy that focuses on alternative drug delivery and improvement of the treatment efficacy while reducing detrimental side effects to normal tissues. Cancer drug resistance is a complicated process that involves multiple mechanisms. Here we discuss the major forms of drug resistance and the new possibilities that nanomedicines offer to overcome these treatment obstacles. Novel nanomedicines that have a high ability for flexible, fast drug design and production based on tumor genetic profiles can be created making drug selection for personal patient treatment much more intensive and effective. This review aims to demonstrate the advantage of the young medical science field, nanomedicine, for overcoming cancer drug resistance. With the advanced design and alternative mechanisms of drug delivery known for different nanodrugs including liposomes, polymer conjugates, micelles, dendrimers, carbon-based, and metallic nanoparticles, overcoming various forms of multi-drug resistance looks promising and opens new horizons for cancer treatment.

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Abbreviations: AML, acute myeloid leukemia; CAM-DR, cell adhesion-mediated drug resistance; CCP, charge-conversion polymer; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CSC, cancer stem cell; EGFR, epidermal growth factor receptor; EPR, enhanced permeability and retention; HIF-1, hypoxia-inducible factor 1; IL-2, interleukin-2; LLL, H_2N-Leu-Leu-Leu-OH; IGF-1R, insulin-like growth factor 1 receptor; mAb, monoclonal antibody; MDR, multidrug resistance; MRP, multidrug-resistance-associated protein; NF-κB, nuclear factor κB; NSCLC, non-small cell lung cancer; PDGFR-β, platelet-derived growth factor receptor-β; PEG, polyethylene glycol; RES, reticuloendothelial system; SDF-1/CXCL12, stromal cell-derived factor 1; siRNA, short interfering RNA; TAT, transactivator of transcription; TfR, transferrin receptor; TG2, tissue transglutaminase; TLR, toll-like receptor; TMZ, temozolomide; TNFα, tumor necrosis factor α.

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1. Introduction

Resistance to antineoplastic chemotherapy is a combined characteristic of the specific drug, the specific tumor, and the specific host whereby the drug is ineffective in controlling the tumor without excessive toxicity.

The problem for the medical oncologist is not simply to find an agent that is cytotoxic but to find one that selectively kills neoplastic cells while preserving the essential host cells and their functions. Were it not for the problem of resistance of human cancer to antineoplastic agents or, conversely, the lack of selectivity of those agents, cancer chemotherapy would have been similar to antibacterial chemotherapy in which complete eradication of infection is regularly observed.

Natural (inherited) or acquired resistance is one of the main problems associated with cancer treatment. Natural resistance refers to the initial unresponsiveness of a tumor to a given drug, and acquired resistance refers to the unresponsiveness that emerges after initial successful treatment.

There are three basic categories of resistance to chemotherapy: kinetic, biochemical, and pharmacologic. Cell kinetics and resistance is a particular problem with many human tumors because certain cells are in a plateau growth phase with a small growth fraction. Strategies to overcome resistance due to cell kinetics include: reduction of the bulk of tumors with surgery or radiotherapy; using combinations to include drugs that affect resting populations (G_0 cells); and scheduling of drugs to prevent phase escape or to synchronize cell populations and increase tumor cell elimination. How cells become resistant biochemically is only partially understood. The major mechanisms of biochemical resistance include the inability of a tumor to convert the drug to its active form, the inactivation of a drug, and the upregulation of the tumor enzymatic repair systems that counteract the tumoricidal action. Cells in this resistance category can decrease drug uptake, increase efflux, change the levels or structure of the intracellular target, reduce intracellular activation, increase inactivation of the drug, or increase the rate of repair of damaged DNA. Another example is multidrug resistance (MDR), also called *pleiotropic drug resistance*, which is a phenomenon whereby treatment with one agent confers resistance not only to that drug and other(s) of its class but also to several other unrelated agents. Pharmaceutical resistance can result from poor tumor blood supply, poor or erratic absorption, increased excretion or catabolism, and drug interactions, which all lead to inadequate blood levels of the drug. One other example of pharmacologic resistance is poor transport of agents into certain body tissues and tumor cells. For instance, tumors of the central nervous system (CNS) or ones that metastasize there should be treated with drugs that achieve effective antitumor concentration in the brain tissue and are also effective against the tumor cell type being treated.

Novel nanomedicines offering flexible and fast drug design and production based on tumor genetic profiles can be created making drug selection for personalized patient treatment much more rational and effective. This review aims to demonstrate the advantages of nanomedicine in overcoming cancer drug resistance.

2. Classes of nanodrugs used to treat cancer and their current clinical status

Nanomedicines are being investigated for their use in anticancer therapies to improve drug delivery, increase the efficacy of treatment, reduce side effects, and overcome drug resistance. The number of studies published under the research topics of "nanomedicine," "nanoscience," and "nanotechnology" has increased exponentially over the past decade with a slight decline in 2012, as shown in Fig. 1. As more nanostructures were discovered and their potentials were better understood, the number of publications increased and reached its peak in 2011. Currently, the knowledge base of nanoparticles is still expanding with an emphasis on safety and efficacy.

2.1. Lipid-based nanoparticles (liposomes)

Liposomes, as shown in Fig. 2A, are lipid based vesicles that have the ability to carry payloads in either an aqueous compartment or embedded in the lipid bilayer. The delivery of these liposomes to cancer cells often relies on passive targeting and is based on the enhanced permeability and retention (EPR) effect, for which a leaky tumor vasculature is necessary [1]. A number of liposomes with the addition of targeting ligands, such as the mAb 2C5 with Doxorubicin (Doxil®) [2] and an anti-HER2 mAb with Paclitaxel [3], are in the preclinical phase, whereas others are already undergoing clinical trials. Advances to liposome design have also been made with the addition of polyethylene glycol (PEG, known as stealth liposomes), which increases circulation time, as well as strategies for a triggered release of the drug once internalized, such as hyperthermia, as is used in ThermoDox®, which is currently in Phase III trials [1,4,5].

2.2. Polymer-based nanoparticles and micelles

Polymeric nanoparticles, as shown in Fig. 2B, can either covalently attach to or encapsulate therapeutic payloads. Biodegradable synthetic and/or natural polymers are used. Through self-assembly after mixing the drug with the polymers, capsules may be formed spontaneously (micelles, Fig. 2C) or by emulsion techniques as nanosized droplets. These nanospheres contain a solid core that is ideal for hydrophobic drugs, are highly stable, have a relatively uniform size, and are capable of controlled drug release. For water-soluble polymers, drugs can be