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Nanotechnology approaches for personalized treatment of multidrug resistant cancers☆,☆☆

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ABSTRACT

The efficacy of chemotherapy is substantially limited by the resistance of cancer cells to anticancer drugs that fluctuates significantly in different patients. Under identical chemotherapeutic protocols, some patients may receive relatively ineffective doses of anticancer agents while other individuals obtain excessive amounts of drugs that induce severe adverse side effects on healthy tissues. The current review is focused on an individualized selection of drugs and targets to suppress multidrug resistance. Such selection is based on the molecular characteristics of a tumor from an individual patient that can potentially improve the treatment outcome and bring us closer to an era of personalized medicine.

Contents

Abbreviations: ABC, adenosine triphosphate (ATP)-binding cassette; ASO, antisense oligonucleotides; CPT, camptothecin; DBD, drug-binding domain; DDS, drug delivery system; DOX, doxorubicin; EPR, enhanced permeability and retention effect; IC_{50} dose, a dose that kills 50% of cells; LHRH, luteinizing hormone-release hormone; NBD, nucleotide-binding domain; NLC, nanostructured lipid carriers; PAMAM, poly(amido amine); siRNA, small interfering RNA; SNP, single-nucleotide polymorphism; TMD, transmembrane domain; TPADDS, targeted proapoptotic drug delivery system.

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1. Introduction

Cancer is one of the most devastating diseases affecting the life of many people around the world. Despite advances in surgical and radiation treatments, chemotherapy continues to be an important therapeutic option for different malignancies, especially for primary advanced and metastatic tumors. However, the efficacy of chemotherapy is substantially limited by the intrinsic and acquired resistance of cancer cells to anticancer drugs [1]. Although several approaches have been recently developed and tested for the suppression of such resistance [2–5], their efficacy fluctuates significantly in different patients due to the wide variations of drug resistance mechanisms among individual patients. Among patients placed in identical chemotherapeutic protocols, some of them may receive relatively ineffective doses of anticancer agents while other individuals obtain excessive amounts of drugs that induce severe adverse side effects on healthy tissues. Hence, the individualized selection of drug doses and targets to suppress resistance based on the molecular characteristics of tumors can potentially improve the treatment outcome and bring us closer to an era of personalized medicine.

The aim of the present review is to describe major mechanisms of drug resistance and approaches to overcome or suppress them with emphasis on personalized selection of drugs and methods of treatment based on the individual genetic profile of patient tumors. Here, we propose a novel approach to the personalized selection of effective treatment for each individual cancer patient based on the genotype and phenotype profiles of the tumor samples obtained from the same patient. We try to establish a correlation between genetic data observed in tumor tissues obtained from patients, their individual resistance to different drugs, and the efficiency of the treatment. It is expected that such a correlation will be established and used for the selection of the most effective treatment for an individual patient. It is expected that the proposed approach will enhance the effectiveness of treatment of primary tumors, prevent the development of metastases, and limit severe adverse side effects on healthy tissues and organs.

2. Mechanisms of multidrug resistance

During the initial phase of chemotherapy, an anticancer drug kills most of the cancer cells. However, not all of the cells are killed. Some cells survive the treatment and initiate further regrowth of cancer cells. In many cases new cancer cells become resistant to the treatment. To overcome the resistance to the previously used drug, a treatment with another drug or combination of several drugs with different mechanisms of action is used [6–9]. However, in the late phase of chemotherapy, cancer cells become resistant not only to the drugs that were previously used for the treatment but to many anticancer drugs with distinct mechanisms of cancer killing. Such type of cellular resistance when tumor cells treated with one anticancer drug become resistant to a whole spectrum of drugs is usually termed as multidrug resistance [5]. Multidrug resistance can be intrinsic or acquired. Important subsets of cancer cells that are notorious for intrinsic drug resistance are called cancer initiating or stem cells [10–14]. These cells overexpress certain stem cell markers, survive treatment with anticancer drug(s), and initiate a growth of new tumor cells that in most cases possess multidrug resistance.

The development of multidrug resistance in cancer cells as other types of adaptation to any stress includes short-term (initial or urgent) and long-term stages. Short-term phase of adaptation arises directly after the irritant starts to act, occurs on the basis of ready, performed biological mechanisms and is incomplete. During this stage the organism functions at the limit of its physiological potential. This initial stage of adaptation usually leads to the more or less pronounced damage of the cells. In contrast, long-term adaptation arises gradually as a result of repeated or long-term environmental action (in case of chemotherapy—prolonged or repeated action of anticancer drug(s)). This type of adaptation of cancer cells to chemotherapy develops on the basis of repeated realization of urgent adaptation. As a result, a cancer cell acquires a new quality: from a drug sensitive cell, a drug resistant cell evolves. The mechanisms used by the cell to avoid death by the specific drug, in many instances render the cell resistant to yet additional drugs that the cell has never being in contact with. Mechanisms of intrinsic and acquired resistance are similar and include two major types of resistance that we termed as “pump” and “nonpump” resistance [15–18] (Fig. 1).

2.1. Pump resistance

Pump resistance depends on membrane-bound active drug efflux pumps that expel anticancer drugs from the cytoplasm out from the cells. Today, many such drug efflux transporters have been identified [19–22] (Fig. 1). The main drug efflux transporters include but are not limited to P-Glycoprotein (encoded in human by the *MDR1* gene), a family of multidrug resistance-associated proteins (MRP), lung resistance proteins (LRP), breast cancer resistance proteins (BCRP), and many others. Active drug efflux systems can be divided into two families. The first family of drug efflux pumps consists of a single transmembrane protein that effluxes drugs by using proton-motive forces. The second family includes the adenosine triphosphate (ATP)-binding cassette (ABC) transporters. The later mechanism is very important in the development of multidrug resistance of cancer. A typical structure of the ABC transporters includes four or five membrane-associated domains (Fig. 2) [23,24]. Two or three domains are highly hydrophobic and each consists of five or six putative transmembrane segments in α-helical configuration. These transmembrane domains (TMD1 and TMD2 in Fig. 2) form the pathway for drug efflux. The other two domains are nucleotide-binding domains (NBD1 and NBD2 in Fig. 2),