Biotechnology Advances xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Biotechnology Advances

journal homepage: www.elsevier.com/locate/biotechadv

Research review paper

Different strategies to overcome multidrug resistance in cancer

Manju Saraswathy, Shaoqin Gong *

Department of Biomedical Engineering, University of Wisconsin–Madison, Madison, WI 53706, USA
Wisconsin Institutes for Discovery, University of Wisconsin–Madison, Madison, WI 53706, USA

ARTICLE INFO

Article history:
Received 14 March 2013
Received in revised form 6 June 2013
Accepted 14 June 2013
Available online xxxx

Keywords:
Cancer
Multidrug resistance
Chemosensitizers
Anticancer agents
Nanocarriers
RNAi therapy

ABSTRACT

The risk of acquisition of resistance to chemotherapy remains a major hurdle in the management of various types of cancer patients. Several cellular and noncellular mechanisms are involved in developing both intrinsic and acquired resistance in cancer cells toward chemotherapy. This review covers the various multidrug resistance (MDR) mechanisms observed in cancer cells as well as the various strategies developed to overcome these MDR mechanisms. Extensive studies have been conducted during the last several decades to enhance the efficacy of chemotherapy by suppressing or evading these MDR mechanisms including the use of new anticancer drugs that could escape from the efflux reaction, MDR modulators or chemosensitizers, multifunctional nanocarriers, and RNA interference (RNAi) therapy.

Contents

1. Introduction

Cancer is a severe health threat. In developed countries, cancer is the second leading cause of death accounting for 21% (2.8 million) of all mortalities. In developing countries, cancer ranks third as a cause of death and accounts for 9.5% (4.8 million) of all deaths. In 2008, approximately 12.7 million new cancer cases and 7.6 million deaths were reported throughout the world. According to the World Health Organization (WHO), by 2050, it is expected that 27 million new cancer cases and 17.5 million cancer deaths will occur per year (http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf, 2012; Jemel et al., 2011). Although there has been tremendous progress over the last few decades in the prevention, detection, and treatment of cancer, the risk of tumors acquiring resistance to chemotherapy (multidrug resistance) remains a major hurdle to the successful treatment of various types of cancers including blood, breast, ovarian, lung, and lower gastrointestinal tract cancers. Multidrug resistance (MDR) is a phenomenon in which cancer cells exhibit a cross-resistant phenotype against multiple unrelated drugs that are structurally and/or functionally different and may also have different molecular targets. Cancer cells may exhibit intrinsic MDR or they may acquire MDR during chemotherapy. For intrinsic MDR, cancer cells exhibit resistance to chemotherapy at their initial exposure to the anticancer

* Corresponding author. Tel.: +1 608 316 4311.
E-mail address: sgong@engr.wisc.edu (S. Gong).

0734-9750/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.biotechadv.2013.06.004

drug. However, in acquired MDR, resistance to chemotherapy occurs during the course of the treatment or upon recurrence of the disease after successful chemotherapy (Baguley, 2010; Gottesman et al., 2002; Lage, 2008; Shaffer et al., 2012; Yague et al., 2007; Yuen and Sikic, 1994). Several host factors are involved in the development of both intrinsic and acquired MDR including those that impair the delivery of anticancer drugs to the cancer cells and nullify their cytotoxic effects, and those that alter the genetic or epigenetic factors of cancer cells, which leads to drug insensitivity. As evident from clinical practice, two or more MDR mechanisms often act simultaneously in each cancer type thereby making treatment more challenging. Extensive studies have been carried out during the last few decades to enhance the efficacy of chemotherapy by suppressing or evading these MDR mechanisms including the use of new anticancer drugs that could escape from efflux reactions, MDR modulators or chemosensitizers, multifunctional nanocarriers, and RNAi therapy (Coley, 2008; Li et al., 2012; Shabbits et al., 2001). This review covers various MDR mechanisms observed in cancer cells as well as various strategies developed to overcome these mechanisms.

2. Mechanisms of multidrug resistance

In clinical practice, MDR becomes a crucial problem when an effective dose of anticancer drug increases to a non-manageable level. Since several factors are involved in the development of both intrinsic and acquired MDR, a clear understanding of these molecular mechanisms is necessary to develop effective treatment modalities. For instance, vascular networks induced by tumor angiogenesis are structurally and functionally abnormal due to the imbalance of angiogenic regulators, such as vascular endothelial growth factor (VEGF) and angiopoietins. Consequently, tumor blood flow is chaotic, which can lead to hypoxic and acidic regions in tumors (Carmeliet and Jain, 2000). Hypoxia in cancer might lead to multidrug resistance via different cellular pathways such as lost sensitivity to p53-mediated apoptosis, and enhanced P-glycoprotein expression (Tredan et al., 2007). A schematic representation of different MDR contributing factors is shown in Fig. 1. To date, the most widely studied MDR mechanisms are those associated with drug efflux mechanisms involving ATP-binding cassette (ABC) membrane transporters (Schinkel and Jonker, 2012; Szakács et al., 2006a, 2006b). In humans, more than 48 MDR genes were identified from the ABC transporter superfamily, among which the most extensively characterized MDR transporters include P-glycoprotein (P-gp/ABCB1), multidrug resistance associated protein-1 (MRP1/ABCC1), and breast cancer resistant proteins (ABCG2) (Giacomini et al., 2010; Stein, 1997). P-gp, a 170 kDa plasma membrane protein encoded by the MDR1 gene, consists of two ATP binding cassettes and two transmembrane regions. P-gp can detect and bind a large variety of anticancer drugs and other hydrophobic compounds including anthracyclines, epipodophyllotoxins, vinca alkaloids, and taxanes. This drug binding activity results in the activation of one of the ATP-binding domains of P-gp and the subsequent hydrolysis of ATP, leading to a major change in the shape of P-gp, which causes expulsion of the drug from the cancer cell. It is evident from the literature that tumors originating from tissues with naturally high levels of P-gp expression may be intrinsically drug resistant (e.g., colon, kidney, pancreas, and liver carcinoma) (Sun et al., 2004). The multidrug resistance associated protein-1 (MRP1 or ABCC1), a 190 kDa protein consisting of 17 transmembrane domains having P-gp like cores, is mainly located in the plasma membrane.

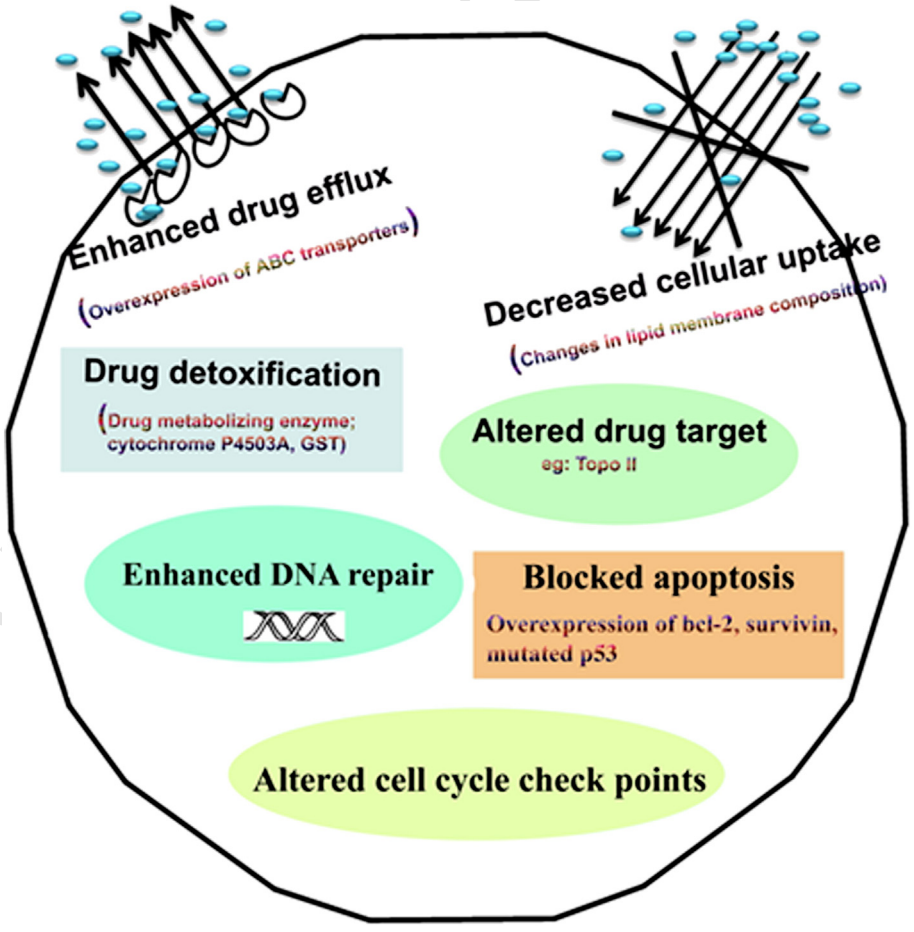

Fig. 1. Schematic representation of different contributing factors of MDR (Gottesman et al., 2002).

Please cite this article as: Saraswathy M, Gong S, Different strategies to overcome multidrug resistance in cancer, Biotechnol Adv (2013), http://dx.doi.org/10.1016/j.biotechadv.2013.06.004