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Research review paper 1

Different strategies to overcome multidrug resistance in cancer 2

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ABSTRACT

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8	Article	history: The risk of acquisition of resistance to chemotherapy remains a major hurdle in the management of various	23		
9	Receiv	ved 14 March 2013 types of cancer patients. Several cellular and noncellular mechanisms are involved in developing both intrin-	types of cancer patients. Several cellular and noncellular mechanisms are involved in developing both intrin- 24 sic and acquired resistance in cancer cells toward chemotherapy. This review covers the various multidrug 25		
10	Receiv	red in revised form 6 June 2013 sic and acquired resistance in cancer cells toward chemotherapy. This review covers the various multidrug			
11	Accept	ted 14 June 2013 resistance (MDR) mechanisms observed in cancer cells as well as the various strategies developed to over-	resistance (MDR) mechanisms observed in cancer cells as well as the various strategies developed to over- 26		
12	Availa	ble online xxxx come these MDR mechanisms. Extensive studies have been conducted during the last several decades to en-	27		
15		hance the efficacy of chemotherapy by suppressing or evaluing these MDR mechanisms including the use of	28		
16	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 Contents 1. Introduction	<i>index</i> the entraction of electronic tapy by suppressing of evaluation including the decision of the second states and the second st	new anticancer drugs that could escape from the efflux reaction MDR modulators or chemosensitizers 20		
17	Cancer	r multifunctional paragrammers and DNA interferences (DNAi) thereas	29		
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1. Introduction 51

Cancer is a severe health threat. In developed countries, cancer is 52the second leading cause of death accounting for 21% (2.8 million) 53of all mortalities. In developing countries, cancer ranks third as a 54cause of death and accounts for 9.5% (4.8 million) of all deaths. In 552008, approximately 12.7 million new cancer cases and 7.6 million 56deaths were reported throughout the world. According to the World 5758 Health Organization (WHO), by 2050, it is expected that 27 million new cancer cases and 17.5 million cancer deaths will occur per year 59

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(http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/ 60 documents/document/acspc-031941.pdf, 2012; Jemel et al., 2011). 61 Although there has been tremendous progress over the last few decades 62 in the prevention, detection, and treatment of cancer, the risk of tumors 63 acquiring resistance to chemotherapy (multidrug resistance) remains a 64 major hurdle to the successful treatment of various types of cancers in- 65 cluding blood, breast, ovarian, lung, and lower gastrointestinal tract can- 66 cers. Multidrug resistance (MDR) is a phenomenon in which cancer cells 67 exhibit a cross-resistant phenotype against multiple unrelated drugs that 68 are structurally and/or functionally different and may also have different 69 molecular targets. Cancer cells may exhibit intrinsic MDR or they may 70 acquire MDR during chemotherapy. For intrinsic MDR, cancer cells exhib-71 it resistance to chemotherapy at their initial exposure to the anticancer 72

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drug. However, in acquired MDR, resistance to chemotherapy occurs dur-73 74 ing the course of the treatment or upon recurrence of the disease after successful chemotherapy (Baguley, 2010; Gottesman et al., 2002; Lage, 75**05**76 2008; Shaffer et al., 2012; Yague et al., 2007; Yuen and Sikic, 1994). Several host factors are involved in the development of both intrinsic 77 and acquired MDR including those that impair the delivery of anticancer 78 79drugs to the cancer cells and nullify their cytotoxic effects, and those that 80 alter the genetic or epigenetic factors of cancer cells, which leads to drug insensitivity. As evident from clinical practice, two or more MDR mecha-81 82 nisms often act simultaneously in each cancer type thereby making treatment more challenging. Extensive studies have been carried out during 83 the last few decades to enhance the efficacy of chemotherapy by sup-84 pressing or evading these MDR mechanisms including the use of new an-85 ticancer drugs that could escape from efflux reactions, MDR modulators 86 or chemosensitizers, multifunctional nanocarriers, and RNAi therapy 87 (Coley, 2008; Li et al., 2012; Shabbits et al., 2001). This review covers var-88 ious MDR mechanisms observed in cancer cells as well as various strate-89 90 gies developed to overcome these mechanisms.

91 **2. Mechanisms of multidrug resistance**

92In clinical practice, MDR becomes a crucial problem when an ef-93 fective dose of anticancer drug increases to a non-manageable level. Since several factors are involved in the development of both intrinsic 94 and acquired MDR, a clear understanding of these molecular mecha-95 nisms is necessary to develop effective treatment modalities. For 96 97 instance, vascular networks induced by tumor angiogenesis are struc-98 turally and functionally abnormal due to the imbalance of angiogenic 99 regulators, such as vascular endothelial growth factor (VEGF) and

angiopoietins. Consequently, tumor blood flow is chaotic, which can 100 lead to hypoxic and acidic regions in tumors (Carmeliet and Jain, 101 2000). Hypoxia in cancer might lead to multidrug resistance via 102 different cellular pathways such as lost sensitivity to p53-mediated 103 apoptosis, and enhanced P-glycoprotein expression (Tredan et al., 104 2007). A schematic representation of different MDR contributing fac- 105 tors is shown in Fig. 1. To date, the most widely studied MDR mecha- 106 nisms are those associated with drug efflux mechanisms involving 107 ATP-binding cassette (ABC) membrane transporters (Schinkel and 108 Jonker, 2012; Szakács et al., 2006a, 2006b). In humans, more than 109 Q6 48 MDR genes were identified from the ABC transporter superfamily, 110 among which the most extensively characterized MDR transporters 111 include P-glycoprotein (P-gp/ABCB1), multidrug resistance associat- 112 ed protein-1 (MRP1/ABCC1), and breast cancer resistant proteins 113 (ABCG2) (Giacomini et al., 2010; Stein, 1997). P-gp, a 170 kDa plasma 114 membrane protein encoded by the MDR1 gene, consists of two ATP 115 binding cassettes and two transmembrane regions. P-gp can detect 116 and bind a large variety of anticancer drugs and other hydrophobic 117 compounds including anthracyclines, epipodophyllotoxins, vinca 118 alkaloids, and taxanes. This drug binding activity results in the activa- 119 tion of one of the ATP-binding domains of P-gp and the subsequent 120 hydrolysis of ATP, leading to a major change in the shape of P-gp, 121 which causes expulsion of the drug from the cancer cell. It is evident 122 from the literature that tumors originating from tissues with natural- 123 ly high levels of P-gp expression may be intrinsically drug resistant 124 (e.g., colon, kidney, pancreas, and liver carcinoma) (Sun et al., 125 2004). The multidrug resistance associated protein-1 (MRP1 or 126 ABCC1), a 190 kDa protein consisting of 17 transmembrane domains 127 having P-gp like cores, is mainly located in the plasma membrane. 128



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

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