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Review

Cancer chemoresistance; biochemical and molecular aspects: a brief overview

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ABSTRACT

The effectiveness of chemotherapy is one of the main challenges in cancer treatment and resistance to classic drugs and traditional treatment processes is an obstacle to this goal. Drug resistance that may be inherent or adventitious can cause poor treatment outcome and tumor relapse. In most cases, resistance to a drug can lead to resistance to many other drugs structure and function of which is not necessarily similar to the first drug. This phenomenon is the main mechanism behind failure of many of metastatic cancers. There are various molecular mechanisms involved in multidrug resistance, including change in the activity of membrane transporters (such as ABC transporters), increase of drug metabolism, change of the target enzyme (such as mutations that change thymidylate synthase and topoisomerases), promotion of DNA damage repair, and escape from drug induced apoptosis. Clinical and laboratory investigations on biomarkers involved in the response to chemotherapy have characterized the key factors behind the failure of treatments. Knowing the molecular factors involved in drug resistance may help us to develop new strategies for more promising chemotherapy and reduce the rate of relapse. In this brief review, molecular mechanisms and tumor microenvironment leading to decreased drug sensitivity, and strategies of reversing drug resistance are described.

Contents

Abbreviations: ABC transporter, ATP-binding cassette transporter; MDR, multidrug resistance; MRP, multidrug resistance-associated protein; cMOAT, canalicular multispecific organic anion transporter; BCRP, breast cancer resistance protein; MXR, mitoxantrone resistance protein; ABC-P, placenta ABC protein; BSEP, bile salt export pump; SPGP, sister of p-glycoprotein; TMD, transmembrane domain; NBD, nucleotide-binding domain; GST, glutathione S-transferase; DPD, dihydropyrimidine dehydrogenase; 5-FU, 5-fluorouracil; FdUMP, fluorodeoxyuridine monophosphate; TS, thymidylate synthase; ERCC1, Excision Repair Cross-Complementing protein group-1; XPE-BF, xeroderma pigmentosum group E binding factor; XPA, xeroderma pigmentosum group A.

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1. Introduction

Among various approaches being used for cancer therapy nowadays, chemotherapy is known to be of the most effectiveness (Szakacs et al., 2006; Rich and Bao, 2007). However development of new chemotherapeutic agents has increased the efficiency of chemotherapy, in most cases inefficacy of the drugs, frequently due to resistance of malignant cells to a variety of chemotherapeutic agents, a phenomenon known as "multidrug resistance", is still a major problem that is challenging particularly in treatment of metastatic cancers (Gottesman, 2002; Corrie, 2008; Krishna and Mayer, 2000).

Resistance to therapeutic agents in cancer patients can be classified in two categories: 1- inherent resistance related to genetic characteristics of the tumor cells that is a protective mechanism for survival in rough environments and, 2- acquired resistance due to exposure to the drugs (Luqmani, 2005; Holohan et al., 2013; Swanton, 2012; Lowe et al., 2004; Chen et al., 2014).

There are various mechanisms involved in multidrug resistance, including reduction of uptake of water-soluble drugs, promotion of DNA damage repair, suppression of apoptosis, increase in hydrophobic drugs efflux, alteration of drug metabolism and cell cycle (Longley and Johnston, 2005; Fojo and Bates, 2003). Increase of drug efflux as a very common mechanism in tumor cells has been studied more and in more detail than other mechanisms.

Identification of mechanisms involved in multidrug resistance can facilitate overcoming this problem and developing novel therapeutics for cancer. This review summarizes the most important information available about molecular mechanisms of chemoresistance and various strategies utilized to suppress these mechanisms. Moreover, Drug resistance mediated by tumor microenvironment will be discussed briefly.

2. Molecular mechanisms of chemoresistance

Regarding the ways tumor cells response to chemotherapy, different mechanisms of drug resistance (Table 1) are categorized in some groups as follow: (Fig. 1).

2.1. ATP-dependent drug efflux

Drug efflux, often resulting from increased efflux of the cytotoxic drugs by cell-membrane transporters, is one of the most common mechanisms of drug resistance in cancer cells. This mechanism decreases intracellular concentrations of anticancer drugs. Increased drug efflux falls in the category of "inherent defenses" and tumor cells use it to escape chemotherapy drugs (Fig. 2) (Gottesman et al., 2002; Vasiliou et al., 2009; Levchenko et al., 2005; Rees et al., 2009). Knowing that target of many anticancer drugs is intracellular, cell-membrane transporters play an important role in multidrug resistance and if they fail in crossing the cell membrane, drugs will be unable to take any action.

The ATP-binding cassette (ABC) transporters are membrane proteins that have considerable clinical importance. To date, there have been 49 different ABC transporter genes found in the human genome.

Table 1
Molecular mechanisms of drug resistance in cancer chemotherapy.

Resistance mechanism	Target	Anti-cancer drug	Cancer type	Reference
ATP-dependent drug efflux	ABC transporters	Most classical chemotherapeutic agents	Most cancers	Fletcher et al., 2010
Increase of drug detoxification	Glutathione	Cisplatin	Primary ovarian cancer	Hamada et al., 1994
	S-transferases	Methotrexate, cisplatin, doxorubicin	Osteosarcoma	Uozaki et al., 1997
	Dihydropyrimidine dehydrogenase	5-FU	Colorectal cancer, head and neck cancer, advanced gastric cancer	Salonga et al., 2000; Etienne et al., 1995; Yamada et al., 2009
Alteration in drug target	Thymidylate synthase	5-FU, leucovorin	Gastric carcinoma, colorectal cancer	Yeh et al., 1998; Leichman et al., 1997
		5-FU	Advanced colorectal cancer	Kamoshida et al., 2004
		Cisplatin, 5- FU	Esophageal Cancer	Joshi et al., 2005
	Estrogen receptor	Tamoxifen	Breast cancer	Johnston et al., 1995
	Topoisomerase-I	Camptothecin	Non-small cell lung cancer	Tsurutani et al., 2002
	Topoisomerase II	Adriamycin	B-cell CLL	Potmesil et al., 1988
Change in DNA damage repair	ERCC1	Platins, paclitaxe	Ovarian cancer	Steffensen et al., 2009
	MLH1	5-FU, leucovorin	Breast cancer	Mackay et al., 2000
		5-FU	Locally advanced rectal cancer	Bertolini et al., 2007
Failure of cell cycle arrest regulation	p53	Cyclophosphamide, epirubicin, methotrexate, 5-5-5-FU, paclitaxel	Breast cancer	Bottini et al., 2000
		Alkylating agents	B-CLL	Sturm et al., 2003
		Anthracyclin-cytosine arabinoside, prednisone, fludarabine	AML, CLL, myelodysplastic syndrome	Wattel et al., 1994
		Cisplatin	Advanced ovarian carcinoma	Righetti et al., 1996
		Platins	Ovarian Cancer	Reles et al., 2001
		5-FU	Metastatic colorectal cancer	Etienne et al., 2002
		Cisplatin, fluorouracil	Head and neck squamous cell carcinoma	Cabelguenne et al., 2000
	BRCA1	Platins, taxanes	Ovarian Carcinoma	Swisher et al., 2008
Alteration in Bcl-2 regulation	Bcl-2	Etoposide, vincristine, doxorubicin and bolus prednisone, cyclophosphamide	Non-Hodgkin's Lymphoma	Wilson et al., 1997
		Cyclophosphamide, methotrexate, 5-FU, tamoxifen	Operable node-positive breast cancer	Gasparini et al., 1995
		Anthracycline, docetaxel, doxorubicin	Breast cancer	Abdel-Fatah et al., 2013; Buchholz et al., 2003
	Bax	Paclitaxel	Ovarian Cancer	Tai et al., 1998
		leucovorin, 5-FU, capecitabine	Rectal carcinoma	Chang, H.J. et al. 2005; Chang, I.Y. et al., 2005