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Mechanisms and relevant genes of drug resistance in gastric cancer

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ABSTRACT

Gastric cancer (GC) is one of the most common malignancies in China, and chemotherapy is an important treatment for GC. However, drug resistance remains the main barrier to successful chemotherapy. Drug resistance is a complex phenomenon resulting from a combination of factors and mechanisms. The number of known relevant genes implicated in this phenomenon is growing rapidly. This review focuses on the mechanisms involved in the occurrence of drug resistance and explores the functions of several relevant genes in GC chemotherapy resistance.

Keywords: chemotherapy, drug resistance, gastric cancer

INTRODUCTION

Gastric cancer (GC) is the fourth most common malignancy in the world and more than 70% of cases occur in developing countries, especially Eastern Asia[1, 2]. Due to certain dietary habits including high-salt diets and a preference for pickled foods, as well as eating disorders, GC is the second most common cancer and represents the second leading cause of cancer death in China[3]. The main treatments for gastric cancer include surgery, chemotherapy, radiotherapy, molecular targeted therapy and so on. The 5-year survival rate of patients with early gastric cancer can reach 95% after surgery. However, gastric cancer is characterized by metastasis and drug resistance, and less than 20 percent of patients with advanced gastric cancer will survive five years[4–5]. Most Chinese GC patients are initially diagnosed with late stage GC because of atypical symptoms in the early stages coupled with uncommon gastroscopy. Chemotherapy plays an important role in perioperative and palliative treatment in GC, but chemotherapy failure is usually caused by drug resistance, leading to shorter overall survival and a poorer quality of life.

GC cell resistance to chemotherapy drugs is divided into two categories, namely: primary drug resistance and multidrug resistance. Primary drug resistance is defined as cancer cells that show resistance to a single chemotherapeutic agent without showing any resistance to other kinds of chemotherapeutics. Multidrug resistance (MDR, also known as cross resistance) occurs when patients develop resistance to multiple agents with different structures and/or mechanisms after prolonged exposure to a single anticancer drug. Drug resistance can also be classified as intrinsic drug resistance and acquired drug resistance. Intrinsic drug resistance indicates patients with a pre-existent drug resistance to a particular chemotherapeutic agent, while acquired drug resistance develops after successful chemotherapeutic treatment. This review briefly probes common mechanisms and relevant genes implicated in GC drug resistance, as well as different molecular modulators employed to reverse cancer drug resistance.

MECHANISMS OF GC DRUG RESISTANCE

Increased drug efflux pumps

Human ATP-binding cassette (ABC) transporters are transmembrane proteins that deliver multitudinous molecules across lipid bilayers. They can obtain

energy by hydrolyzation of ATP to carry anticancer drugs, resulting in decreasing intracellular drug concentrations or a varied drug distribution. At least 12 members of the ABC superfamily are connected with drug resistance in laboratory studies, while only three transporters have been confirmed in multiple studies as playing chemoresistant roles *in vivo*, which include: P-glycoprotein (P-gp/ABCB1/MDR1), multidrug resistance protein 1 (MRP1/ABCC1), and breast cancer resistance protein (BCRP/ABCG2)[6]. In addition to ABC transporters, lung resistance protein (LRP) is also an integral membrane protein related to drug resistance, but does not require ATP. It is reported that drug efflux pumps greatly influence GC cell drug resistance[7–8].(***Fig. 1***)
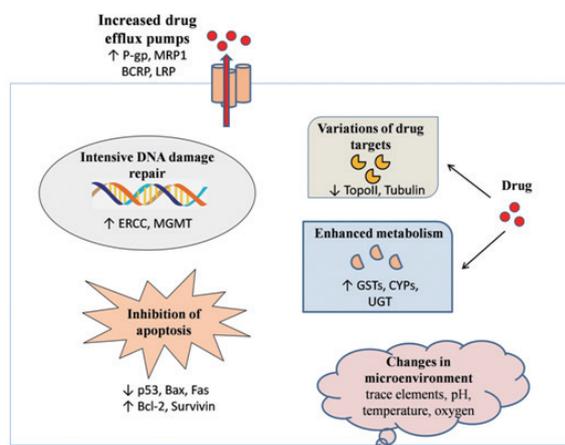

Fig. 1 **Mechanisms and relevant genes implicated in GC drug resistance.**

Enhanced metabolism to drugs

Some enzymes can transform external toxins or intermediates into innocuous substances, rendering anticancer drugs inactive to cancer cells. The most common enzymes involved in drug metabolism include glutathione-S-transferases (GSTs), cytochrome P450s (CYPs), and uridine diphosphate glucuronosyltransferase (UGT). CYPs can convert hydrophobic compounds into inactive polar products suitable for excretion via the kidneys[9]. UGTs can catalyze the inactivation of cytotoxic drugs through the formation of hydrophilic conjugates[10]. Some CYP and GST isoenzymes have been confirmed to be overexpressed in GC tissues, which may promote gastric carcinoma MDR [11].

Variations of drug targets

Chemotherapeutic efficacy depends to a large extent on the profusion of target molecules. Target protein mutation or decreased expression often represents declining chemosensitivity in human cancer. Topoisomerase Ⅱ (Topo Ⅱ) is an important cell proliferation regulator and has been confirmed as the target of many structurally diverse antitumor drugs[12], as quantitative and qualitative changes in Topo Ⅱ have been found to significantly influence cancer cell drug resistance . Tubulin is the target of paclitaxel, which can inhibit spindle formation, and any changes in tubulins will affect tumor tolerance to paclitaxel therapy[13]. The expressions of TopoII and tubulin are related to chemosensitivity in gastric cancer[14, 15].

Intensive DNA damage repair

Cancer cells are able to strengthen DNA repair which help the cell withstand the effects of chemotherapeutics (which conversely acts by suppressing tumors by directly or indirectly damaging cellular DNA). Excision repair cross-complementation (ERCC) genes play a vital role in nucleotide excision repair. The ERCC1－XPF nuclease is encoded by ERCC1 and ERCC4 which not only nicks on the 5′ side of the damaged DNA strand but also repairs DNA interstrand crosslinks[16]. O^6-methylguanine DNA methyltransferase (MGMT) can repair the damaged DNA by inducing the demethylation of O^6-methylguanine, which is caused by alkylating agents[17]. Due to this mechanism, DNA repair genes are able to impair chemotherapeutic effectiveness in GC patients[18].

Inhibition of apoptosis

The therapeutic outcome of chemotherapy largely depends on the reaction of the cells′ apoptotic mechanism, namely if the chemotherapeutic drugs have damaged the DNA irrevocably. There are two drug resistance mechanisms induced by apoptotic inhibition: low expression of apoptotic genes and overexpression of antiapoptotic genes. The former mainly involves p53, Bax and Fas, and the latter consists of Bcl-2, survivin and others. P53 is a tumor suppressor gene prone to mutation, which induces cell apoptosis and activates apoptosis-inducing factors like Fas and Bax[19]. Fas is a member of the tumor necrosis factor superfamily, and the low expressed Fas (or the lack of its receptor) can inhibit cell apoptosis[20]. Survivin belongs to the apoptotic inhibitory protein family and its role is to interdict apoptotic processes by directly inhibiting caspase 3 and caspase 7[21]. Apoptosis related genes greatly regulate the drug resistance of GC cells[22–24].

Changes in cell microenvironment

Trace elements such as calcium, zinc and selenium can affect the sensitivity of cancer cells to chemo-

therapeutic drugs through a variety of pathways. Furthermore, pH, temperature, oxygen concentration and substrate nutrient conditions also make a difference to drug resistance.

GENES RELATED TO GC DRUG RESISTANCE

P-gp

P-gp is a 170 kDa phosphorylated transmembrane glycoprotein encoded by MDR1/ABC and MDR3/ABCB4, which maps to the long arm of chromosome 7q21. P-gp consists of 1 280 amino acids, including two tandem repeat sequences and one joining region. Each tandem repeat sequence is composed of six hydrophobic transmembrane alpha helixes and one hydrophilic nucleotide binding domain(NBD). (containing two ATP binding sites) which can provide energy for transport by hydrolyzing ATP.

P-gp shows prominent expression in excretory tissues and at physiological barriers, including: the gastrointestinal tract, the renal proximal tubule, and the blood-brain barrier. P-gp expression is higher in GC tissues than in neighboring tissues, and increased P-gp protein levels in GC have been associated with increased differentiation and lymph node metastasis[25]. P-gp transports a wide range of electroneutral or electropositive hydrophobic compounds including taxol, vincristine, etoposide, and many others that are clinically indispensable in cancer treatment[26–28]. The clinical application of P-gp inhibitors has always been an area of hot research, but there are several negative factors: the insufficient affinity and specificity of the inhibitors; compensatory adjustment of optional drug transporters; transporter polymorphisms in patients; and the expression of P-gp in normal tissues.

MRP1

MRP1 is a 190 kDa transmembrane protein with significant substrate overlap with P-gp. The MRP1 gene is located on chromosome 16p13.1, and the MRP1 gene encodes the 1 531amino acid protein. MRP1 is made up of three membrane-spanning domains (MSD_0, MSD_1 and MSD_2) and two NBDs. MSD_1 and MSD_2 which constitute the pore through which substrates are transported.

MRP1 is widely distributed in normal tissues, particularly the testicles, kidney and placenta, and can be detected in subcellular organelles. MRP1 expression in GC tissues is higher than that in matched paracarcinoma tissues[29]. MRP1 transports many clinical chemotherapeutics: etoposide, irinotecan, methotrexate, doxorubicin, vincristine, and mitoxantrone[30–31]. While several P-gp inhibitors tested in adult cancers

can also suppress MRP1, few specific inhibitors for MRP1 have been evaluated clinically. Cyclohexyl-linked tricyclic isoxazoles and flavonoid derivatives show selectivity for MRP1, but more clinical studies need to be done to confirm these results[32–33].

BCRP

BCRP is a 72 kDa protein consisting of 665 amino acids. Its encoding gene maps to chromosome 4q22. BCRP monomers have only one NBD and one MSD; therefore, BCRP is a half-transporter. Haider *et al*. proved that BCRP functions as homodimers in the[34] of membrane.

As a universal marker of stem cells, BCRP is widely found in the stem cells of all major tissues[35]. BCRP is also expressed in the intestine, liver, blood-brain barrier, and other tissues. Expression of BCRP is upregulated in GC compared with adjacent non-neoplastic tissue and is implicated in carcinoma differentiation[36]. Substrates of BCRP include: mitoxantrone, camptothecin analogs, aminopterin, and others. Furthermore, BCRP can inhibit the effects of prazosin and glibenclamide[37]. Fumitremorgin C, elacridar, tyrosine kinase inhibitors, and many other BCRP inhibitors have been reported, but few small molecule modulators have shown promising effects in clinical trials[38].

LRP

LRP is a 110 kDa protein originally identified in lung cancer MDR cell lines. The LRP gene is located on chromosome 16p11.2 with high similarity to genes of major vault proteins in slime molds and brown mice. LRP is distributed in the nuclear pore complex(NPC) and cytoplasm[39, 40]. There are two potential mechanisms of LRP-mediated drug resistance: ① LRP prevents anticancer drugs from entering the nucleus through the NPC and pumps out drugs in the nucleus; and ② LRP takes part in vesicular transport to remove chemotherapeutics.

LRP is mainly involved in secretion in the epithelium. The level of expression of LRP in GC tissues is higher than in noncancerous tissues, however LRP has not been correlated with clinical and/or pathological characteristics of GC[41]. Overexpression of LRP reduces cancer cell sensitivity to doxorubicin, etoposide, vincristine, paclitaxel, and cisplatinum. Cyclosporin A, hydrogen epoxy methylquinone, tyroservatide, as well as many other agents can regulate LRP expression, but reversing LRP-mediated drug resistance clinically will require greater effort[42].

GSTs

GSTs belong to the phase Ⅱ detoxification enzyme

group and consist of seven subclasses (α, μ, π, θ, κ, σ, and ζ). GSTs catalyze the conjugation of glutathione (GSH) with a broad range of electrophilic exogenous substrates. The direct catalytic action on drug metabolites (rather than on the parent drugs) lowers reactivity and increases the water solubility of these drugs[43]. In addition, GSTs regulate cell apoptosis by inhibiting the JNK signaling pathway[44].

GSTs are expressed in a wide range of normal tissues, and different tissues express different levels of GST isoenzymes. GSTπ is the most highly expressed GST isoenzyme in cancer tissues[45]. The expression level of GSTπ in GC tissues is higher than in normal tissues, and the expression of GSTπ is connected with tumor invasion and lymphatic metastasis[46]. Anticarcinogens that can be detoxified by GSTπ include chlorambucil, cis-platinum, mitoxantrone, cyclophosphamide, and others[43]. Etacrynic acid is an earlier example of a GST inhibitor. Etacrynic acid can increase the sensitivity of tumors to alkylating agents; however, serious side effects (such as diuresis) hamper the clinical application of this molecule[47]. GSH analogues like TER199 (which are competitive inhibitors of both GSH and GSTs) can also induce cancer cell apoptosis through the MAPK pathway, but can also cause bone marrow hyperplasia, limiting the utility of these inhibitors[48]. NBDHEX and its analogues are immune to drug pumps, even those that are highly expressed (particularly the analogues MC3165 and MC3181, which show higher specificity and water solubility) have the potential to be used as oral GST π inhibitors[49–51].

Topo Ⅱ

Mammalian Topo Ⅱ is divided into Topo Ⅱ α (170 kDa) and Topo Ⅱ β (180 kDa), encoded on chromosomes 17q21-22 and 3p24, respectively. Topo Ⅱ forms cleavable complexes with DNA to catalyze DNA untwisting. Anticancer drugs targeting Topo Ⅱ induce single or double-strand breaks by inhibiting Topo Ⅱ catalytic activity (Topo Ⅱ inhibitor) or prolonging the half-life of DNA-Topo Ⅱ complex (Topo Ⅱ toxicant).

Topo Ⅱ α is mainly distributed in proliferating the cell nucleoplasm, and Topo Ⅱ β is widely found in the nucleolus of almost all cells. Expression levels of Topo Ⅱ in normal gastric mucosal tissues is lower than in GC tumors, and the expression of Topo Ⅱ is associated with tumor differentiation and lymphatic metastasis[52].Topo Ⅱ is an important target for many tumor chemotherapeutics used in clinic. Topo Ⅱ inhibitors include aclarubicin, merbarone, ICRF-193 and others.

Topo Ⅱ toxicants include etoposide, doxorubicin, mitoxantrone, as well as other similar agents[53]. With the potential to reverse MDR and reduce side effects, the combination of anticancer drugs that can inhibit both topoI and topo Ⅱ has become a hot area of research.

Bcl-2 and Bax

The Bcl-2 protein family plays an important role in regulating apoptosis through the intrinsic mitochondrial apoptotic pathway. Bcl-2 is a common pro-survival protein, whereas Bax is a member of the pro-apoptotic Bcl-2 family. When Bcl-2 is in the majority, heterodimers consist of Bcl-2 and Bax, preventing Bax from damaging mitochondria. When Bax is dominant, homodimers made up of Bax can damage mitochondrial membrane structures and promote the release of pro-apoptotic factors, leading to cell apoptosis.

The expression level of Bcl-2 in precancerous tissues is significantly lower than that in GC tissues; conversely Bax shows a higher expression level in precancerous tissues[54]. In gastric tumors, the expression level of Bcl-2 is inversely connected with the apoptotic index while Bax behaves the opposite way[55]. Bcl-2 inhibitors, such as ABT-737and S-055746, have been studied in clinical trials, and ABT-199 (venetoclax) has been approved for the treatment of 17p-deleted CLL patients[56]. Several direct Bax activators (including Bim, SAHB, BAM7, and SMBAs) have been identified to effectively induce Bax-mediated apoptosis *in vitro* and *in vivo* but their clinical application is still a long way off[57].

CONCLUSION AND FUTURE PERSPECTIVES

Progress has been made in our understanding of the mechanisms involved in GC chemotherapy resistance, and the functions of numerous resistance-related genes have been investigated in the last decades. However, the universal mechanisms of GC chemotherapy resistance are still unclear, and the understanding of complex interactions between drug-resistant molecules will require more researches. The manipulation of resistance-related genes has enormous potential to mitigate GC drug resistance, however most molecular inhibitors targeting drug-resistant proteins show poor therapeutic efficacy due to specificity, pharmacokinetics, as well as other factors. More comprehensive investigations into drug resistance are encouraged, and will undoubtedly contribute to the development of anticancer drugs and the optimization of chemotherapy regimens. Drug resistance in GC will most likely be greatly improved with future research.

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