

Cellular and Molecular Mechanisms of Chemoresistance for Gastric Cancer

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Abstract: Gastric cancer (GC) is one of the most common malignant tumors in the digestive tract, and chemotherapy plays an irreplaceable role in the comprehensive treatment of GC. However, chemoresistance makes it difficult for patients with GC to benefit steadily from chemotherapy in the long term, which ultimately leads to tumor recurrence, metastasis, and patient death. Elucidating the detailed mechanism of chemoresistance in GC and identifying specific therapeutic targets will help to solve the difficult problem of chemoresistance and improve the prognosis of patients with GC. This review summarizes and clarifies the cellular and molecular mechanisms underlying chemoresistance for GC.

Keywords: gastric cancer, chemoresistance, cellular mechanisms, molecular mechanisms

Introduction

Gastric cancer (GC) is one of the most common malignant tumors in the digestive tract and seriously threatens human life and health. According to statistics, there were more than 1,089,103 new GC cases and 768,793 GC-induced deaths in 2020 worldwide, ranking fifth in morbidity and fourth in mortality among all cancer types.¹ In China, more than 509,421 new GC cases and 400,415 GC-induced deaths were recorded in 2022, ranking third in both morbidity and mortality among all cancer types.² At present, surgery is still the most important treatment for resectable GC.³ Although comprehensive and individualized treatment based on surgery, chemoradiotherapy, targeted therapy and immunotherapy have been widely used in the treatment of GC, the overall efficacy is still not satisfactory. The 5-year survival rate of GC patients is only about 44.5%, and for patients with distant metastasis, it is only about 8.4%.⁴ Chemotherapy plays an irreplaceable role in the comprehensive treatment of GC. However, chemoresistance makes it difficult for GC patients to benefit steadily from chemotherapy in the long term. According to related reports, the proportion of GC patients resistant to chemotherapy is about 46% to 80%.^{5,6} For GC, chemotherapy regimens including XELOX (oxaliplatin plus capecitabine), SOX (S-1 plus oxaliplatin) and FOLFOX (oxaliplatin plus leucovorin and 5-fluorouracil) have been widely used in the clinical treatment.^{7,8} But their efficacy is relatively limited and more than 95% GC patients fail chemotherapy with the progression of chemoresistance, which ultimately leads to tumor recurrence, metastasis, and patient death.⁹ Chemoresistance of GC cells can be divided into primary drug resistance and acquired drug resistance, primary drug resistance means that GC cells possess genetic characteristics of natural drug resistance to various chemotherapeutic drugs, while acquired drug resistance refers to drug resistance produced by GC cells after long-term or repeated action of chemotherapeutic drugs.¹⁰ Currently, most information about chemoresistance of GC cells is obtained from vitro experimental studies, and researchers have revealed a number of mechanisms of chemoresistance.^{11–13} This review summarizes and clarifies the cellular and molecular mechanisms of chemoresistance for GC, aiming at providing a reference for solving the difficult problem of chemoresistance.

Mechanisms of Chemoresistance for GC Drug Efflux Mediated by Membrane Proteins

Abnormally high expression of drug resistance related membrane proteins in cancer cells is one of the main causes of chemoresistance. The basic mechanism is that membrane proteins pump intracellular chemotherapeutic drugs out of the cells through an active energy-consuming mode or keep the drugs in membranous organelles. Thus, the drug concentration in cancer cells can be significantly reduced or their distribution can be effectively changed, leading to drug resistance in cancer cells.¹⁴ This type of membrane proteins is mainly ATP-mediated ABC family related cell membrane transporters, and the representative proteins are P-glycoprotein (P-gp) and multi-drug resistance-associated protein 1 (MRP1).¹⁵

P-gp is an active transmembrane transporter that is dependent on ATP and has the property of a channel protein. With the participation of ATP, P-gp can effectively bind to and pump out intracellular chemotherapeutic drugs, so that the effective concentration of chemotherapeutic drugs inside cancer cells was significantly reduced, leading to drug resistance.^{16,17} Xu et al found that the expression level of P-gp in chemotherapy-resistant GC tissues was significantly higher than that in chemotherapy-sensitive GC tissues, suggesting that P-gp was closely related to multi-drug resistance of GC, and the chemotherapy effect of GC patients with high P-gp expression was relatively poor.¹⁸ Wu et al pointed out that the expression level of P-gp in GC tissues was positively correlated with the expression level of PD-1, and PD-1/PD-L1 could enhance the resistance of GC cells to cisplatin by regulating the PI3K/AKT pathway to increase the expression of P-gp.¹⁹ EGCG could inhibit GC cells growth by inhibiting TFAP2A/VEGF pathway and down-regulating P-gp expression, and then reversed the resistance of GC cells to 5-fluorouracil.²⁰ Sunitinib could significantly enhance the cytotoxicity of adriamycin, vincristine, etoposide, 5-fluorouracil and cisplatin on drug-resistant GC cells, the main mechanism of which was that sunitinib inhibited P-gp function and reversed multi-drug resistance of GC cells.²¹

MRP1 is another classic ATP-dependent transmembrane protein, which is closely related to chemoresistance of GC.^{22,23} The mechanism of chemoresistance of MRP1 is similar to that of P-gp, as following: (1) Excreting intracellular chemotherapeutic drugs out of cells through active energy dissipation, thus significantly reducing the content of chemotherapeutic drugs in cancer cells; (2) Transferring chemotherapeutic drugs from the cell nucleus to the cytoplasm, or transferring chemotherapeutic drugs to other subcellular structures (such as lysosomes, etc.), thus affecting the distribution of chemotherapeutic drugs in cancer cells and changing their sites of action.^{24,25} Yan et al showed that HOTAIR could directly bind and inhibit the expression of miR-126, then promote the expression of VEGFA and PIK3R2, and activate the PI3K/AKT/MRP1 pathway, ultimately leading to cisplatin resistance in GC.²⁶ Kong et al believed that Siva-1 could increase the levels of NF- κ B, MDR1 and MRP1, promote the growth and proliferation of GC cells, and significantly reduce the sensitivity of GC cells to vincristine, 5-fluorouracil and adriamycin.²⁷ Wang et al confirmed that SGO1 could increase the efflux of chemotherapeutic drugs and inhibit drug-induced apoptosis by regulating MRP1, Bcl-2 and Bax genes, thereby promoting resistance of GC cells to vincristine, adriamycin, 5-fluorouracil and cisplatin.²⁸ Guo et al pointed out that Runx3 could inhibit the activity of MRP1 promoter in GC cells, and overexpression of Runx3 could inhibit MRP1 and increase the sensibility of GC cells to chemotherapeutic drugs.²⁹

Drug Metabolism and Degradation Mediated by Enzymes

With the participation of enzymes, chemotherapeutic drugs are metabolized or degraded, which is an important mechanism of chemoresistance in cancer cells. These enzymes mainly include glutathione-S-transferases (GSTs), uridine diphospho-glucuronosyl transferases, dihydropyrimidine dehydrogenases, and so on. GSTs play an important role in the chemoresistance of GC cells.^{30,31} GSTs are the most important enzymes involved in the regulation of glutathione binding in vivo, mainly distributed in the cytoplasm, and is closely related to the self-renewal and metabolic detoxification of cells as well as the drug resistance of cancer cells.³² Studies have shown that GSTs were highly expressed in tissues and cells of various malignant tumors such as GC, lung cancer and ovarian cancer, and could significantly reduce the toxicity of chemotherapeutic drugs through metabolic detoxification, thus leading to drug resistance of cancer cells.^{33–35} Further studies have shown that GSTs could regulate the nucleophilic attack of glutathione on chemotherapeutic drugs, catalyze the effective binding of chemotherapeutic drugs with glutathione and increase their water solubility, thus enable the excretion of chemotherapeutic drugs through bile or kidney, and ultimately help cancer cells effectively escape the toxic

effect of chemotherapeutic drugs.^{32,36} Therefore, the higher the expression level and activity of intracellular GSTs, the more drug degradation and excretion, the stronger the resistance of cancer cells to chemotherapeutic drugs. Geng et al found that the expression level of GST- π was significantly increased in GC cells resistant to 5-fluorouracil, cisplatin and mitomycin, suggesting that the detection of GST- π can be used as a predictor of the use chemotherapeutic drugs for GC, so the detection of GST- π had certain guiding significance for the formulation of reasonable chemotherapy regimen for GC patients.³⁷ Zhang et al pointed out that TRAIL could inhibit the growth and increase the apoptosis of GC cells by reducing the expression of drug resistance genes MDR1, LRP and GST- π , thus participating in the reversal of multi-drug resistance in GC.³⁸

Reinforcement of DNA Repair

Changes in the internal environment of the body or interference from external factors such as radiation may cause DNA damage, which may lead to slowing down of cell proliferation, stagnation of differentiation, increasing of cell senescence and apoptosis, or even cell canceration. Targeted DNA damage is one of the main mechanisms of many chemotherapeutic drugs, but some cancer cells can develop drug-resistant phenotypes by enhancing DNA repair or countering DNA damage.^{39,40} Studies have shown that excision repair cross-complementing gene 1 (ERCC1) is one of the core members of DNA repair and is closely related to drug resistance in cancer cells. Up-regulation of ERCC1 could promote DNA repair in cancer cells and led to drug-resistance.^{41,42} Song et al pointed out that the levels of miR-122 and ERCC1 in GC samples were negatively correlated, and decreasing the expression of miR-122 may induce cisplatin resistance by increasing the expression of ERCC1.⁴³ Yeh et al pointed out that overexpression of ERCC1 was an independent predictor for the efficacy of mFOLFOX-4 neoadjuvant chemotherapy for GC patients, which could not only predict response but also the progression-free survival and overall survival.⁴⁴ De et al maintained that the expression of ERCC1 could predict the benefit of platinum chemotherapy after GC surgery. For ERCC1-positive patients, a non-platinum chemotherapy regimen should be considered first, while ERCC1-negative GC patients have relatively good effects on platinum chemotherapeutic drugs.⁴⁵ In addition, DNA topoisomerase II and O6-methylguanine-DNA methyltransferase are also key enzymes involved in DNA replication and repair, and the abnormal expression or dysfunction of these enzymes can also lead to enhancing DNA repair and chemoresistance.^{46,47}

Intensification of Epithelial-Mesenchymal Transition

Epithelial-mesenchymal transition (EMT) refers to the process of phenotypic transformation of epithelial-like cells into mesenchymal cells.⁴⁸ After EMT, cancer cells acquire the morphological characteristics of mesenchymal cells, the cell polarity disappears, and the connection with the basement membrane is lost. Thus, cancer cells can achieve higher migration and transfer ability after EMT. At the molecular level, EMT includes changes in various cell adhesion molecules, such as up-regulation of N-cadherin expression, down-regulation of E-cadherin, and increased expression of matrix metalloproteinase-2, etc.⁴⁹ EMT is closely related to the chemoresistance of GC cells.⁵⁰ Huang et al pointed out that transcription factor Snail is mainly involved in the regulation of the EMT process, and the expression of Snail was significantly up-regulated in cisplatin-resistant MGC803 and AGS cells, which have typical EMT characteristics. Down-regulation of HER2 expression could cause Snail expression to be down-regulated and reverse the EMT of GC cells, thus improving the sensitivity of GC cells to cisplatin.⁵¹ The expression level of eIF5A2 was negatively correlated with the sensitivity of cisplatin to GC cells, and it could promote the drug resistance of GC cells to cisplatin by inducing EMT, while silencing eIF5A2 could reverse the drug resistance effect of GC cells to cisplatin, so eIF5A2 may be a novel molecular target for GC.⁵² The expression of WTAP in GC tissues was significantly increased, and its high expression was closely related to poor prognosis of GC patients. WTAP could promote EMT of GC cells and enhance their resistance to cisplatin and cyclophosphamide by enhancing TGF- β expression.⁵³ The expression of ADAR1 in human GC tissues was significantly higher than that in paracancer tissues, and the expression of EMT-related marker proteins such as vimentin, n-cadherin, β -catenin, MMP9, MMP2 and TWIST can be decreased by knockdown of ADAR1. Knockout of ADAR1 could inhibit the metastasis of GC cells and reverse cisplatin resistance in GC cells, which could improve the therapeutic effect of cisplatin on GC.⁵⁴

Inhibition of Apoptosis

Apoptosis refers to programmed cell death, which is a physiological or pathological phenomenon regulated by various pro-apoptotic and anti-apoptotic genes in eukaryotic cells. Inhibition of apoptosis is one of the classical mechanisms of drug resistance in cancer cells, which mainly by activating the expression of anti-apoptotic genes and inhibiting the activity of pro-apoptotic genes. P53 and Bcl-2 family genes are the main apoptosis-related genes.⁵⁵

P53 gene is the most classical regulatory gene of apoptosis, which regulates the cell cycle, inhibits cell division and proliferation, and promotes cell apoptosis.⁵⁶ Wild-type P53 gene has a negative regulatory relationship with MDR1 gene, while mutant P53 gene loses its negative regulatory effect on MDR1. Therefore, mutant P53 gene can lead to the activation of MDR1 gene expression, which leads to drug resistance of cancer cells.⁵⁷ When GC cells are subjected to chemotherapeutic drugs, wild-type P53 gene can inhibit cell proliferation and induce apoptosis, and then enhance the sensitivity of GC cells to chemotherapeutic drugs, while mutant P53 gene loses the functions of apoptosis induction and cell cycle arrest, resulting in a significant increase in drug resistance of GC cells.⁵⁸ Studies have shown that Acetyl-keto-beta boswellic acid could induce apoptosis by P53 pathway and increase the sensitivity of GC cells to cisplatin.⁵⁹ HZ08 could increase the expression and activity of P53, and inhibit the negative regulatory factors of P53, thereby inducing cell apoptosis and ultimately reversing the resistance of GC cells to cisplatin.⁶⁰

Bcl-2 family genes are involved in the regulation of apoptosis, including apoptosis-activating genes (such as Bax and Bcl-xs) and apoptosis-inhibiting genes (such as Bcl-xl and Bcl-2).⁶¹ Studies have shown that Bcl-2 is the main factor of RhogDI2-mediated cisplatin resistance in GC cells, and overexpression of Bcl-2 can effectively prevent cisplatin induced apoptosis in GC cells and increase drug resistance.⁶² By regulating the expression of Bcl-2 and Bax, SGO1 could inhibit apoptosis, thereby enabling GC cells to acquire multi-drug resistance. Silencing SOG1 could improve the sensitivity of GC cells to adriamycin and 5-fluorouracil.²⁸ Overexpression of transcription factor TWIST not only increased the migration and invasion of GC cells but also increased the resistance of GC cells to paclitaxel. The main mechanism was that TWIST increased the inhibitory effect of Bcl-2.⁶³ Evading apoptosis is a hallmark of cancer cells, inducing apoptosis is a promising therapeutic strategy, and Bcl-xl is a potential drug target for GC.⁶⁴

Reinforcement of Autophagy

Autophagy refers to the process in which the double-layer membrane shed from the rough endoplasmic reticulum wraps the degraded organelles and proteins in cells to form autophagosomes, which fuse with lysosomes to form autophagolysosomes and degrade cell metabolites to achieve cell self-renewal.⁶⁵ Autophagy in physiological state can maintain cell homeostasis. Under the conditions of drug toxicity, oxidative stress, nutrient deficiency, ischemia, hypoxia, and radiation, high levels of autophagy occur in cells to ensure their survival.^{66,67} Autophagy in cancer cells is significantly enhanced when they are subjected to the toxic action of chemotherapeutic drugs, resulting in drug resistance. Inhibition of autophagy will help promoting apoptosis and reducing drug resistance of cancer cells.^{68,69} When GC cells were treated with 5-fluorouracil, the cells sensitive to 5-fluorouracil entered the process of apoptosis and the cells died, while the cells resistant to 5-fluorouracil enter the process of autophagy and the cells still survive.⁷⁰ Studies have shown that TRIM14 could promote the autophagy of GC cells by regulating AMPK/mTOR pathway and increase their resistance to chemotherapeutic drugs, so TRIM14/AMPK/mTOR pathway and its related molecules may be novel targets for GC treatment.⁷¹ METase could reduce the resistance of GC cells to cisplatin by regulating HULC/FoxM1 pathway to inhibit autophagy, and upregulating the expression of METase could help increasing the sensitivity of GC cells to cisplatin.⁷² LncRNA EIF3J-DT could block ATG14 mRNA degradation by competitively binding miRNA188-3p, enhance ATG14 mRNA stability, activate GC cell autophagy, and induce GC cell drug resistance. In addition, both LncRNA EIF3J-DT and ATG14 were highly expressed in chemotherapy resistant GC tissues; therefore, GC patients with high expression of LncRNA EIF3J-DT have poor chemotherapy effects.⁷³

Changes in Tumor Microenvironment

Cell microenvironment, such as oxygen pressure, microorganisms, trace elements, pH, and nutritional conditions, have a significant impact on the drug response of cancer cells.^{74–76} Hypoxia is a common phenomenon in solid tumors.

Hypoxia can affect the expression of drug resistance genes such as hypoxia inducible factor-1 α (HIF-1 α), P53 and MDR1, thus leading to drug resistance in cancer cells. In addition, the growth of tumor blood vessels is slowed down and the distribution of blood vessels is sparse during hypoxia, which further makes it difficult for chemotherapeutic drugs to be delivered to cancer tissues and play an anticancer effect.⁷⁷ HIF-1 α is an important regulatory gene of hypoxia, and up-regulated expression of HIF-1 α could promote the resistance of GC cells to cisplatin and paclitaxel.^{78,79} Chen et al found that baicalein could inhibit glycolysis and Akt phosphorylation induced by hypoxia, thereby reducing the expression of HIF-1 α in GC cells and reversing 5-fluorouracil resistance induced by hypoxia.⁸⁰ Studies have shown that *Helicobacter pylori* is an important cause of GC, and CagA protein secreted by *Helicobacter pylori* is positively correlated with 5-fluorouracil resistance in GC.⁸¹ While microRNA-320a and microRNA-4496 could reduce the chemoresistance of GC cells induced by CagA protein secreted by *Helicobacter pylori* according to targeting β -catenin and ATP binding boxes.⁸² In terms of trace elements, the levels of zinc, chromium and manganese in GC tissues were significantly higher than those in adjacent normal tissues.⁸³ Moreover, trace elements are closely related to *Helicobacter pylori* infection, apoptosis inhibition and oxidative stress, which can affect the effect of GC cells on chemotherapeutic drugs.^{84,85}

Effect of Cancer Stem Cell

Cancer stem cells are very few cells in various malignant tumor cells with unlimited self-renewal potential and play an important role in the survival, proliferation, recurrence, metastasis, and drug resistance of cancer cells.^{86,87} During chemotherapy, cancer stem cells are resistant and enriched, and then proliferate after dormancy, leading to subsequent tumor recurrence and metastasis. GC stem cells can regulate drug resistance of GC cells by affecting drug metabolism, apoptosis, DNA damage, EMT and tumor microenvironment.⁸⁸ Xu et al pointed out that chemoresistance of GC is mainly caused by GC stem cells, and the co-expression of CD44(+)/Musashi-1(+) can be used to identify GC stem cells, and the GC cells of CD44(+)/Musashi-1(+) can significantly resist adriamycin-induced apoptosis, showing strong drug resistance.⁸⁹ Lgr5-positive GC cells have the characteristics of GC stem cells and could promote cisplatin resistance by regulating SIRT1/CREB/ABCG2 signaling pathway.⁹⁰ Ukai et al analyzed 5-fluorouracil resistant GC cells and found that KHDRBS3 could promote GC cells to acquire the characteristics of stem cells by regulating the expression of CD44, thus leading to GC cells resistant to 5-fluorouracil.⁹¹ ID-1 plays an important role in tumor progression and the formation of GC stem cells. By targeting Nanog and Oct-4, knockout of ID1 could reduce the self-renewal characteristics similar to stem cells in normal GC cells, thereby reducing the proliferation of GC cells and the resistance to cisplatin.⁹² GC stem cells are important causes of GC recurrence, metastasis and drug resistance, and inducing differentiation of GC stem cells is a novel therapeutic strategy to reverse drug resistance of GC cells.^{93,94}

Regulation of Non-Coding RNAs and Exosomes

In recent years, non-coding RNAs, such as miRNAs, lncRNAs, and circRNAs, have been widely studied for their role in the chemoresistance of GC. In terms of miRNA, studies have shown that miR-15a-5p could increase cisplatin resistance in GC cells by inhibiting the expression of PHLPP2 and enhancing the phosphorylation of downstream gene Akt, and serum level of miR-15a-5p was significantly correlated with the sensitivity of GC cells to oxaliplatin.⁹⁵ miR-301b-3p could promote the resistance of GC cells to cisplatin and vincristine by inhibiting TXNIP, and P-gp may participate in this resistance process regulated by miR-301b-3p.⁹⁶ In terms of lncRNA, Hang et al reported that Notch 1 could promote cisplatin resistance of GC cells through up-regulation of lncRNA AK022798, the main mechanism of which was up-regulation of MRP1 and P-gp and reduction of apoptosis.⁹⁷ lncRNA EIF3J-DT was highly expressed in GC-resistant cells, which could induce GC cells resistant to platinum and fluorouracil by regulating ATG14 expression and activating autophagy.⁷³ In terms of circRNA, Zhong et al pointed out that circ_0032821 could regulate the expression of SOX9 and induce oxaliplatin resistance in GC cells, and silenced the expression of circ_0032821 could inhibit the growth of transplanted GC tumor in mice.⁹⁸ In cisplatin resistant GC cells, circ-PVT1 was up-regulated while miR-30a-5p was down-regulated. Knocking down of circ-PVT1 could promote the apoptosis of GC cells by promoting the expression of miR-30a-5p and inhibit their resistance to cisplatin.⁹⁹

Exosomes have also received special attention as a research hotspot. Studies have shown that M2-type polarized macrophages and their derived exosomes could activate the PI3K/AKT signaling pathway and confer cisplatin resistance

in GC cells.¹⁰⁰ Exosome-mediated CLIC1 expression could promote the resistance of GC cells to vincristine, mainly by upregulating P-gp and Bcl-2 expression.¹⁰¹ Ohzawa et al pointed out that the ratio of miRNAs in peritoneal exosomes is an effective indicator for predicting the effect of intraperitoneal chemotherapy in patients with GC peritoneal metastasis, and patients with a higher ratio of miR-21/miR-29b or miR-223/miR-29b had poor intraperitoneal chemotherapy effect and poor prognosis.¹⁰²

Summary and Future Outlook

In summary, significant progress has been made in the research on the cellular and molecular mechanisms of chemoresistance for GC, which mainly includes the following aspects (Figure 1): (1) accelerating drug efflux by membrane proteins and reducing the concentration of intracellular chemotherapeutic drugs; (2) accelerating drug metabolism and degradation by oxidoreductases and reducing the toxicity of chemotherapeutic drugs; (3) promoting DNA repair and maintaining the continuous proliferation of GC cells; (4) promoting the EMT of GC cells and maintaining their proliferation and migration ability; (5) inhibiting apoptosis of GC cells; (6) increasing autophagy of GC cells; (7) changing the microenvironment of GC cells, such as hypoxia, microorganisms, and trace elements; (8) effect of GC stem cells; and (9) regulation by non-coding RNAs and exosomes. Although many molecules and mechanisms have been identified to be involved in the chemoresistance of GC, current studies are mostly experimental. In addition, tumors have complex tissue structures in vivo, so the mechanisms of chemoresistance may be more complex.

When we understand these mechanisms of chemoresistance for GC, we have the prospect to overcome chemoresistance of GC, which means that we can conduct more experimental and clinical studies on these resistance mechanisms, so as to carry out effective clinical transformation and develop new targeted drugs. At present, there are two ways to overcome chemoresistance of GC. Firstly, some scholars suggest using natural products instead of traditional chemotherapy drugs to fight GC. For example, natural products such as curcumin, loganetin, and houttuynia cordata thumb, are

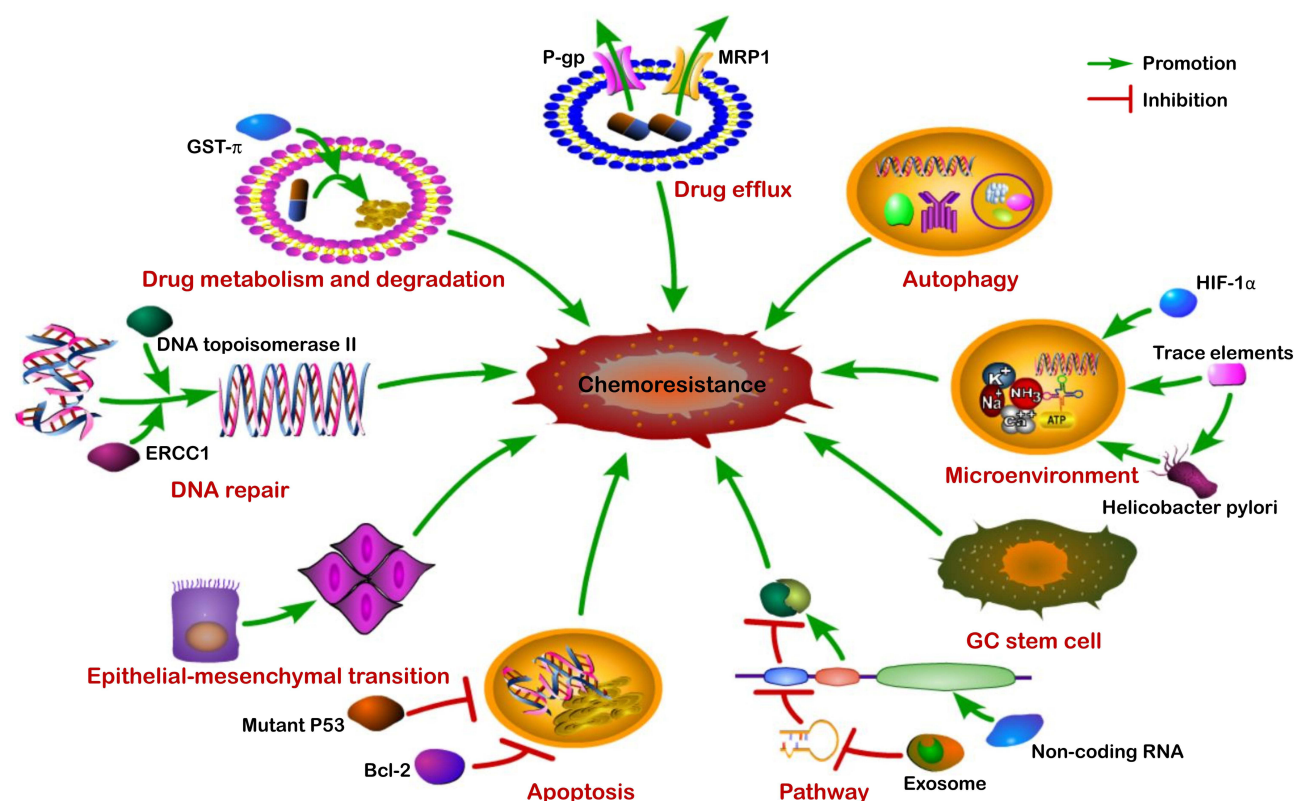


Figure 1 Cellular and molecular mechanisms of chemoresistance for GC.

Abbreviations: GC, gastric cancer; P-gp, P-glycoprotein; MRP1, multi-drug resistance-associated protein 1; GST-π, glutathione-S-transferase π; DNA, deoxyribonucleic acid; RNA, Ribonucleic Acid; ERCC1, excision repair cross-complementing gene 1; P53, protein 53; Bcl-2, B-cell lymphoma-2; HIF-1α, hypoxia inducible factor-1α.

very effective in the treatment of GC.^{103–105} Secondly, combined therapy, which means combining two or more methods from chemotherapy, targeted therapy, and immunotherapy, can significantly improve the efficacy of GC treatment.^{106,107} More hopefully in the future, targeting drug-tolerant cells, which is the latest hot research on cancer treatment, maybe become a promising strategy for overcoming acquired chemoresistance of GC.^{108,109}

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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