International Journal of General Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Cellular and Molecular Mechanisms of Chemoresistance for Gastric Cancer

Zonglin Li[1,*], Xingming Shu[1,*], Xin Liu[1], Qiuyun Li[2], Yifu Hu[2], Bingbing Jia[2], Min Song[3]

[1]Department of General Surgery (Gastrointestinal Surgery), The Affiliated Hospital of Southwest Medical University, Luzhou, People's Republic of China; [2]Grade 2023, Clinical Medicine College, Southwest Medical University, Luzhou, People's Republic of China; [3]Department of Laboratory Medicine, The Affiliated Hospital of Southwest Medical University, Luzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Min Song, Department of Laboratory Medicine, The Affiliated Hospital of Southwest Medical University, Luzhou, 646000, People's Republic of China, Tel +8615883059785, Email songminlele2007@126.com

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.

Received: 14 April 2024
Accepted: 23 August 2024
Published: 29 August 2024

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) Transfering chemotherapeutic drugs from the cell nucleus to the cytoplasm, or transfering 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-κB, 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 autophago-lysosomes 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-1α (HIF-1α), 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-1α is an important regulatory gene of hypoxia, and up-regulated expression of HIF-1α 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-1α 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 resistant 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 inducting 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

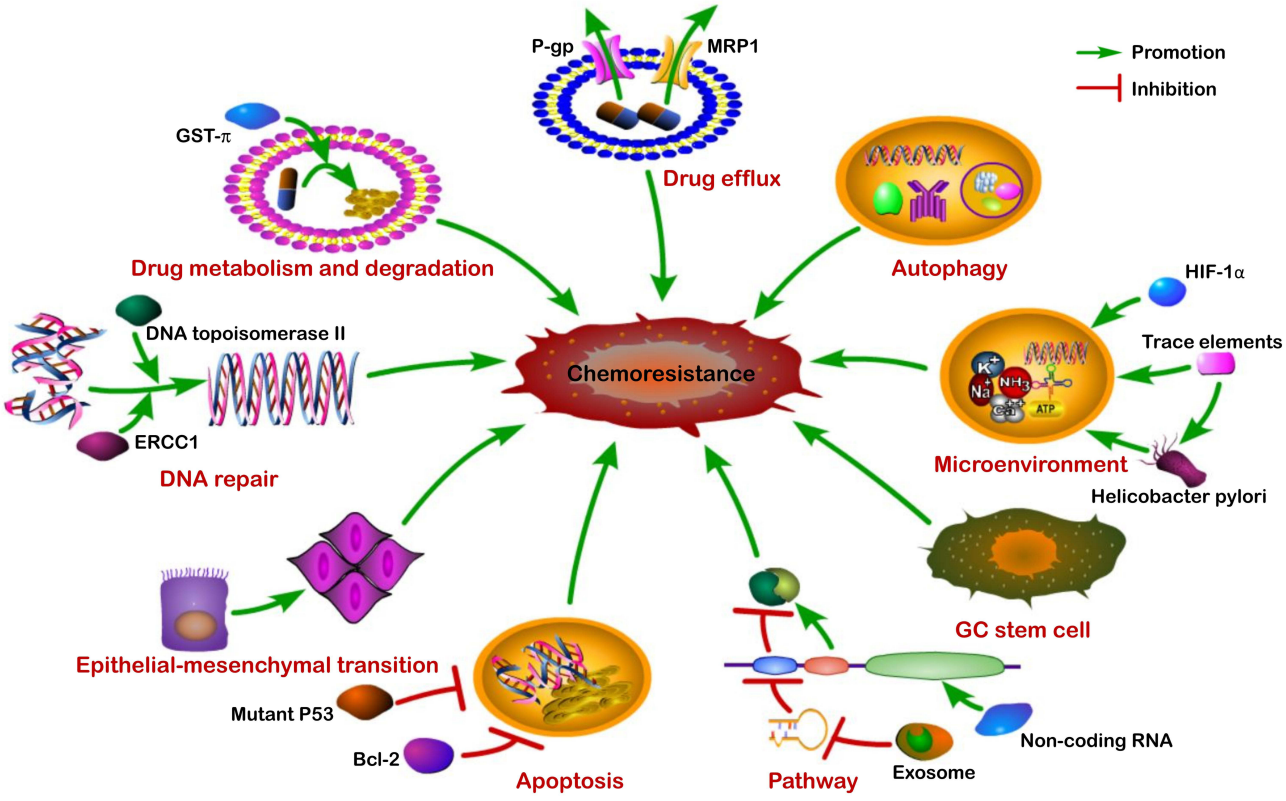

Figure 1 Cellular and molecular mechanisms of chemoresistance for GC.
Abbreviations: *GC*, gastric cancer; *P-gp*, P-glycoprotein; *MRP1*, multi-drug resistance-associated protein 1; *GST-π*, glutathione-S-transferase π; *DNA*, deoxyribonucleic acid; *RNA*, Ribonucleic Acid; *ERCC1*, excision repair 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] Secondarily, combined therapy, which means combining two or more methods from chemotherapy, targeted therapy, and immunotherapy, can significantly improves 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.

Funding

This work was supported by (1) Sichuan Science and Technology Program (No.2023YFS0320); (2) Luzhou Science and Technology Program (No.2022-JYJ-135); (3) Doctoral Research Initiation Fund of Affiliated Hospital of Southwest Medical University.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Xia C, Dong X, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J*. 2022;135 (5):584–590. doi:10.1097/CM9.0000000000002108
3. Song M, Jiang Y, Liu Y, Li Z. Safety and efficacy of partial omentectomy in laparoscopic distal gastrectomy for pt3-t4a stage gastric cancer. *Int J Gen Med*. 2023;16:4681–4690. doi:10.2147/IJGM.S434090
4. Li H, Zhang H, Zhang H, Wang Y, Wang X, Hou H. Survival of gastric cancer in China from 2000 to 2022: a nationwide systematic review of hospital-based studies. *J Glob Health*. 2022;12:11014. doi:10.7189/jogh.12.11014
5. De Vita F, Orditura M, Matano E, et al. A Phase II study of biweekly oxaliplatin plus infusional 5-fluorouracil and folinic acid (folfox-4) as first-line treatment of advanced gastric cancer patients. *Br J Cancer*. 2005;92(9):1644–1649. doi:10.1038/sj.bjc.6602573
6. Zhang F, Zhang Y, Jia Z, Wu H, Gu K. Oxaliplatin-based regimen is superior to cisplatin-based regimen in tumour remission as first-line chemotherapy for advanced gastric cancer: a meta-analysis. *J Cancer*. 2019;10(8):1923–1929. doi:10.7150/jca.28896
7. Yin X, Fang T, Wang Y, et al. Efficacy of postoperative folfox versus xelox chemotherapy for gastric cancer and prognostic value of platelet-lymphocyte ratio in patients receiving xelox. *Front Oncol*. 2020;10:584772. doi:10.3389/fonc.2020.584772
8. Liu X, Yan Y, Lu L, et al. Comparison of sox and capox in patients with advanced gastric cancer after laparoscopic d2 gastrectomy: a randomized controlled trial. *Cancer Med*. 2024;13(11):e7326. doi:10.1002/cam4.7326
9. Marin JJ, Al-Abdulla R, Lozano E, et al. Mechanisms of resistance to chemotherapy in gastric cancer. *Anticancer Agents Med Chem*. 2016;16 (3):318–334. doi:10.2174/1871520615666150803125121
10. Luo YJ, Huang QM, Ren Y, et al. Non-coding RNA in drug resistance of gastric cancer. *World J Gastrointest Oncol*. 2019;11(11):957–970. doi:10.4251/wjgo.v11.i11.957
11. Li Z, Lu M, Zhou Y, et al. Role of long non-coding RNAs in the chemoresistance of gastric cancer: a systematic review. *Onco Targets Ther*. 2021;14:503–518. doi:10.2147/OTT.S294378
12. Dai X, Chen Y, Chen N, et al. Klf5-mediated aquaporin 3 activated autophagy to facilitate cisplatin resistance of gastric cancer. *Immunopharm Immunotox*. 2023;45(2):140–152. doi:10.1080/08923973.2022.2122498
13. Zhao Z, Zhu Y. Fap, cd10, and gpr77-labeled cafs cause neoadjuvant chemotherapy resistance by inducing emt and csc in gastric cancer. *Bmc Cancer*. 2023;23(1):507. doi:10.1186/s12885-023-11011-0
14. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The different mechanisms of cancer drug resistance: a brief review. *Adv Pharm Bull*. 2017;7(3):339–348. doi:10.15171/apb.2017.041
15. Pote MS, Gacche RN. Atp-binding cassette efflux transporters and mdr in cancer. *Drug Discov Today*. 2023;28(5):103537. doi:10.1016/j.drudis.2023.103537
16. Elmeliegy M, Vourvahis M, Guo C, Wang DD. Effect of p-glycoprotein (p-gp) inducers on exposure of p-gp substrates: review of clinical drug-drug interaction studies. *Clin Pharmacokinet*. 2020;59(6):699–714. doi:10.1007/s40262-020-00867-1
17. Tanigawara Y. Role of p-glycoprotein in drug disposition. *Ther Drug Monit*. 2000;22(1):137–140. doi:10.1097/00007691-200002000-00029
18. Xu HW, Xu L, Hao JH, Qin CY, Liu H. Expression of p-glycoprotein and multidrug resistance-associated protein is associated with multidrug resistance in gastric cancer. *J Int Med Res*. 2010;38(1):34–42. doi:10.1177/147323001003800104
19. Wu L, Cai S, Deng Y, et al. Pd-1/pd-l1 enhanced cisplatin resistance in gastric cancer through pi3k/akt mediated p-gp expression. *Int Immunopharmacol*. 2021;94:107443. doi:10.1016/j.intimp.2021.107443

20. Tang H, Zeng L, Wang J, et al. Reversal of 5-fluorouracil resistance by EGCG is mediate by inactivation of TFAP2A/VEGF signaling pathway and down-regulation of mdr-1 and p-gp expression in gastric cancer. *Oncotarget*. 2017;8(47):82842–82853. doi:10.18632/oncotarget.20666
21. Zhang Y, Wang Q. Sunitinib reverse multidrug resistance in gastric cancer cells by modulating stat3 and inhibiting p-gp function. *Cell Biochem Biophys*. 2013;67(2):575–581. doi:10.1007/s12013-013-9544-5
22. Abe T, Mori T, Hori S, Koike K, Kuwano M. multidrug resistance protein (mrp). *Nihon Rinsho*. 1997;55(5):1077–1082.
23. Endo K, Maehara Y, Kusumoto T, Ichiyoshi Y, Kuwano M, Sugimachi K. Expression of multidrug-resistance-associated protein (mrp) and chemosensitivity in human gastric cancer. *Int J Cancer*. 1996;68(3):372–377. doi:10.1002/(SICI)1097-0215(19961104)68:3<372::AID-IJC16>3.0.CO;2-A
24. Wang JQ, Yang Y, Cai CY, et al. Multidrug resistance proteins (MRPs): structure, function and the overcoming of cancer multidrug resistance. *Drug Resist Updat*. 2021;54:100743. doi:10.1016/j.drup.2021.100743
25. Zhang YK, Wang YJ, Gupta P, Chen ZS. Multidrug resistance proteins (MRPs) and cancer therapy. *Aaps J*. 2015;17(4):802–812. doi:10.1208/s12248-015-9757-1
26. Yan J, Dang Y, Liu S, Zhang Y, Zhang G. Lncrna hotair promotes cisplatin resistance in gastric cancer by targeting mir-126 to activate the pi3k/akt/mrp1 genes. *Tumour Biol*. 2016;37(12):16345–16355. doi:10.1007/s13277-016-5448-5
27. Kong FB, Deng QM, Deng HQ, et al. Siva-1 regulates multidrug resistance of gastric cancer by targeting mdr1 and mrp1 via the nf-kappab pathway. *Mol Med Rep*. 2020;22(2):1558–1566. doi:10.3892/mmr.2020.11211
28. Wang Y, Liu L, Liu X, et al. Shugoshin1 enhances multidrug resistance of gastric cancer cells by regulating mrp1, bcl-2, and bax genes. *Tumour Biol*. 2013;34(4):2205–2214. doi:10.1007/s13277-013-0758-3
29. Guo C, Ding J, Yao L, et al. Tumor suppressor gene runx3 sensitizes gastric cancer cells to chemotherapeutic drugs by downregulating bcl-2, mdr-1 and mrp-1. *Int J Cancer*. 2005;116(1):155–160. doi:10.1002/ijc.20919
30. Pathania S, Bhatia R, Baldi A, Singh R, Rawal RK. Drug metabolizing enzymes and their inhibitors' role in cancer resistance. *Biomed Pharmacother*. 2018;105:53–65. doi:10.1016/j.biopha.2018.05.117
31. Verma H, Singh Bahia M, Choudhary S, Kumar Singh P, Silakari O. Drug metabolizing enzymes-associated chemo resistance and strategies to overcome it. *Drug Metab Rev*. 2019;51(1/4):196–223. doi:10.1080/03602532.2019.1632886
32. Chatterjee A, Gupta S. The multifaceted role of glutathione s-transferases in cancer. *Cancer Lett*. 2018;433:33–42. doi:10.1016/j.canlet.2018.06.028
33. Monden N, Abe S, Sutoh I, Hishikawa Y, Kinugasa S, Nagasue N. Prognostic significance of the expressions of metallothionein, glutathione-s-transferase-pi, and p-glycoprotein in curatively resected gastric cancer. *Oncology*. 1997;54(5):391–399. doi:10.1159/000227725
34. Wang W, Wei J, Tu X, Ye X. Potential role of gst-pi in lung cancer stem cell cisplatin resistance. *Biomed Res Int*. 2021;2021:9142364. doi:10.1155/2021/9142364
35. Tong X, Zhao J, Zhang Y, Mu P, Wang X. Expression levels of mrp1, gst-pi, and gsk3beta in ovarian cancer and the relationship with drug resistance and prognosis of patients. *Oncol Lett*. 2019;18(1):22–28. doi:10.3892/ol.2019.10315
36. Singh RR, Reindl KM. Glutathione s-transferases in cancer. *Antioxidants*. 2021;10(5). doi:10.3390/antiox10050701
37. Geng M, Wang L, Chen X, Cao R, Li P. The association between chemosensitivity and pgp, gst-pi and topo ii expression in gastric cancer. *Diagn Pathol*. 2013;8(1):198. doi:10.1186/1746-1596-8-198
38. Zhang KG, Qin CY, Wang HQ, Wang JX, Wang QM. The effect of trail on the expression of multidrug resistant genes mdr1, lrp and gst-pi in drug-resistant gastric cancer cell sgc7901/vcr. *Hepatogastroenterology*. 2012;59(120):2672–2676. doi:10.5754/hge11850
39. Li LY, Guan YD, Chen XS, Yang JM, Cheng Y. DNA repair pathways in cancer therapy and resistance. *Front Pharmacol*. 2020;11:629266. doi:10.3389/fphar.2020.629266
40. Sethy C, Kundu CN. 5-fluorouracil (5-FU) resistance and the new strategy to enhance the sensitivity against cancer: implication of DNA repair inhibition. *Biomed Pharmacother*. 2021;137:111285. doi:10.1016/j.biopha.2021.111285
41. Huang MY, Huang JJ, Huang CM, et al. Relationship between expression of proteins ercc1, ercc2, and xrcc1 and clinical outcomes in patients with rectal cancer treated with folfox-based preoperative chemoradiotherapy. *World J Surg*. 2017;41(11):2884–2897. doi:10.1007/s00268-017-4070-z
42. Villalobos M, Czapiewski P, Reinmuth N, et al. Ercc1 assessment in upfront treatment with and without cisplatin-based chemotherapy in stage iiib/iv non-squamous non-small cell lung cancer. *Med Oncol*. 2018;35(7):106. doi:10.1007/s12032-018-1169-5
43. Song A, Zhao L, Wang Y, He D, Li Y. Chemoresistance in gastric cancer is attributed to the overexpression of excision repair cross-complementing 1 (ercc1) caused by microRNA-122 dysregulation. *J Cell Physiol*. 2019;234(12 Pt.1):22485–22492. doi:10.1002/jcp.28812
44. Yeh YS, Chen YT, Tsai HL, et al. Predictive value of ercc1, ercc2, and xrcc expression for patients with locally advanced or metastatic gastric cancer treated with neoadjuvant mfolfox-4 chemotherapy. *Pathol Oncol Res*. 2020;26(2):1105–1116. doi:10.1007/s12253-019-00666-5
45. De Dosso S, Zanellato E, Nucifora M, et al. Ercc1 predicts outcome in patients with gastric cancer treated with adjuvant cisplatin-based chemotherapy. *Cancer Chemother Pharmacol*. 2013;72(1):159–165. doi:10.1007/s00280-013-2181-2
46. Cao Y, Liu H, Li H, et al. Association of O6-methylguanine-DNA methyltransferase protein expression with postoperative prognosis and adjuvant chemotherapeutic benefits among patients with stage ii or iii gastric cancer. *JAMA Surg*. 2017;152(11):e173120. doi:10.1001/jamasurg.2017.3120
47. Chikamori K, Grozav AG, Kozuki T, Grabowski D, Ganapathi R, Ganapathi MK. DNA topoisomerase ii enzymes as molecular targets for cancer chemotherapy. *Curr Cancer Drug Targets*. 2010;10(7):758–771. doi:10.2174/156800910793605785
48. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell*. 2009;139(5):871–890. doi:10.1016/j.cell.2009.11.007
49. Li M, Bu X, Cai B, et al. Biological role of metabolic reprogramming of cancer cells during epithelial-mesenchymal transition (review). *Oncol Rep*. 2019;41(2):727–741. doi:10.3892/or.2018.6882
50. Huang L, Wu RL, Xu AM. Epithelial-mesenchymal transition in gastric cancer. *Am J Transl Res*. 2015;7(11):2141–2158.
51. Huang D, Duan H, Huang H, et al. Cisplatin resistance in gastric cancer cells is associated with her2 upregulation-induced epithelial-mesenchymal transition. *Sci Rep*. 2016;6(1):20502. doi:10.1038/srep20502

52. Sun J, Xu Z, Lv H, et al. Eif5a2 regulates the resistance of gastric cancer cells to cisplatin via induction of emt. *Am J Transl Res*. 2018;10 (12):4269–4279.
53. Liu Y, Da M. Wilms tumor 1 associated protein promotes epithelial mesenchymal transition of gastric cancer cells by accelerating tgf-beta and enhances chemoradiotherapy resistance. *J Cancer Res Clin Oncol*. 2023;149(7):3977–3988. doi:10.1007/s00432-022-04320-7
54. Wang H, Yang L, Liu R, He H, Zhang M, Xu Y. Adar1 affects gastric cancer cell metastasis and reverses cisplatin resistance through azin1. *Anticancer Drugs*. 2023;34(10):1132–1145. doi:10.1097/CAD.0000000000001516
55. Neophytou CM, Trougakos IP, Erin N, Papageorgis P. Apoptosis deregulation and the development of cancer multi-drug resistance. *Cancers*. 2021;13(17). doi:10.3390/cancers13174363
56. Cao L, Zhao S, Yang Q, et al. Chidamide combined with doxorubicin induced p53-driven cell cycle arrest and cell apoptosis reverse multidrug resistance of breast cancer. *Front Oncol*. 2021;11:614458. doi:10.3389/fonc.2021.614458
57. Tsou SH, Hou MH, Hsu LC, Chen TM, Chen YH. Gain-of-function p53 mutant with 21-bp deletion confers susceptibility to multidrug resistance in mcf-7 cells. *Int J Mol Med*. 2016;37(1):233–242. doi:10.3892/ijmm.2015.2406
58. Xie XY, Tan YJ, Zhu YL. relation between mutant p53 and multidrug resistance in gastric cancer. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2006;35(1):91–98. doi:10.3785/j.issn.1008-9292.2006.01.017
59. Al-Bahlani S, Burney IA, Al-Dhahli B, et al. Boswellic acid sensitizes gastric cancer cells to cisplatin-induced apoptosis via p53-mediated pathway. *Bmc Pharmacol Toxicol*. 2020;21(1):64. doi:10.1186/s40360-020-00442-1
60. Tang X, Hu G, Xu C, et al. Hz08 reverse the aneuploidy-induced cisplatin-resistance in gastric cancer by modulating the p53 pathway. *Eur J Pharmacol*. 2013;720(1–3):84–97. doi:10.1016/j.ejphar.2013.10.045
61. Warren C, Wong-Brown MW, Bowden NA. Bcl-2 family isoforms in apoptosis and cancer. *Cell Death Dis*. 2019;10(3):177. doi:10.1038/s41419-019-1407-6
62. Cho HJ, Baek KE, Park SM, et al. Rhogdi2 confers gastric cancer cells resistance against cisplatin-induced apoptosis by upregulation of bcl-2 expression. *Cancer Lett*. 2011;311(1):48–56. doi:10.1016/j.canlet.2011.06.024
63. Kwon CH, Park HJ, Choi Y, Won YJ, Lee SJ, Park DY. Twist mediates resistance to paclitaxel by regulating akt and bcl-2 expression in gastric cancer cells. *Tumour Biol*. 2017;39(10):1393367594. doi:10.1177/1010428317722070
64. Wei Y, Zhang L, Wang C, et al. Anti-apoptotic protein bcl-xl as a therapeutic vulnerability in gastric cancer. *Animal Model Exp Med*. 2023;6 (3):245–254. doi:10.1002/ame2.12330
65. Wollert T. Autophagy. *Curr Biol*. 2019;29(14):R671–R677. doi:10.1016/j.cub.2019.06.014
66. Ichimiya T, Yamakawa T, Hirano T, et al. Autophagy and autophagy-related diseases: a review. *Int J Mol Sci*. 2020;21(23):8974. doi:10.3390/ijms21238974
67. Raj S, Chandel V, Kumar A, et al. Molecular mechanisms of interplay between autophagy and metabolism in cancer. *Life Sci*. 2020;259:118184. doi:10.1016/j.lfs.2020.118184
68. Ma S, Kong D, Fu X, et al. P53-induced autophagy regulates chemotherapy and radiotherapy resistance in multidrug resistance cancer cells. *Dose Resp*. 2021;19(4):1485797998. doi:10.1177/15593258211048046
69. Kumar A, Singh UK, Chaudhary A. Targeting autophagy to overcome drug resistance in cancer therapy. *Future Med Chem*. 2015;7 (12):1535–1542. doi:10.4155/fmc.15.88
70. Li LQ, Xie WJ, Pan D, Chen H, Zhang L. Inhibition of autophagy by bafilomycin a1 promotes chemosensitivity of gastric cancer cells. *Tumour Biol*. 2016;37(1):653–659. doi:10.1007/s13277-015-3842-z
71. Xiao F, Ouyang B, Zou J, Yang Y, Yi L, Yan H. Trim14 promotes autophagy and chemotherapy resistance of gastric cancer cells by regulating AMPK/mTOR pathway. *Drug Dev Res*. 2020;81(5):544–550. doi:10.1002/ddr.21650
72. Xin L, Zhou Q, Yuan YW, et al. Metase/lncrna hulc/foxm1 reduced cisplatin resistance in gastric cancer by suppressing autophagy. *J Cancer Res Clin Oncol*. 2019;145(10):2507–2517. doi:10.1007/s00432-019-03015-w
73. Luo Y, Zheng S, Wu Q, et al. Long noncoding RNA (lncRNA) eif3j-dt induces chemoresistance of gastric cancer via autophagy activation. *Autophagy*. 2021;17(12):4083–4101. doi:10.1080/15548627.2021.1901204
74. Oya Y, Hayakawa Y, Koike K. Tumor microenvironment in gastric cancers. *Cancer Sci*. 2020;111(8):2696–2707. doi:10.1111/cas.14521
75. Montenegro F, Indraccolo S. Metabolism in the tumor microenvironment. *Adv Exp Med Biol*. 2020;1263:1–11. doi:10.1007/978-3-030-44518-8_1
76. Zhao LY, Mei JX, Yu G, et al. Role of the gut microbiota in anticancer therapy: from molecular mechanisms to clinical applications. *Signal Transduct Target Ther*. 2023;8(1):201. doi:10.1038/s41392-023-01406-7
77. Kim JY, Lee JY. Targeting tumor adaption to chronic hypoxia: implications for drug resistance, and how it can be overcome. *Int J Mol Sci*. 2017;18(9):1854. doi:10.3390/ijms18091854
78. Sun XP, Dong X, Lin L, et al. Up-regulation of survivin by akt and hypoxia-inducible factor 1alpha contributes to cisplatin resistance in gastric cancer. *Febs J*. 2014;281(1):115–128. doi:10.1111/febs.12577
79. Fushida S, Okazaki M, Kinoshita J, Yamaguchi T, Ohta T. Impact of hif-1alpha and pkm1 expression on acquisition of paclitaxel resistance in gastric cancer. *Ann Oncol*. 2018;29(Supl.5):v5. doi:10.1093/annonc/mdy151.015
80. Chen F, Zhuang M, Zhong C, et al. Baicalein reverses hypoxia-induced 5-fu resistance in gastric cancer ags cells through suppression of glycolysis and the PTEN/Akt/HIF-1alpha signaling pathway. *Oncol Rep*. 2015;33(1):457–463. doi:10.3892/or.2014.3550
81. Gao S, Song D, Liu Y, Yan H, Chen X. Helicobacter pylori caga protein attenuates 5-fu sensitivity of gastric cancer cells through upregulating cellular glucose metabolism. *Onco Targets Ther*. 2020;13:6339–6349. doi:10.2147/OTT.S230875
82. Kang DW, Yang ES, Noh YN, et al. microRNA-320a and microRNA-4496 attenuate helicobacter pylori cytotoxin-associated gene a (caga)-induced cancer-initiating potential and chemoresistance by targeting beta-catenin and atp-binding cassette, subfamily g, member 2. *J Pathol*. 2017;241(5):614–625. doi:10.1002/path.4866
83. Sohrabi M, Nikkhah M, Sohrabi M, et al. Evaluating tissue levels of the eight trace elements and heavy metals among esophagus and gastric cancer patients: a comparison between cancerous and non-cancerous tissues. *J Trace Elem Med Biol*. 2021;68:126761. doi:10.1016/j.jtemb.2021.126761
84. Dovhanj J, Kljaic K, Vcev A, Ilakovac V. Helicobacter pylori and trace elements. *Clin Lab*. 2010;56(3–4):137–142.

85. Safarzad M, Besharat S, Salimi S, Azarhoush R, Behnampour N, Joshaghani HR. Association between selenium, cadmium, and arsenic levels and genetic polymorphisms in DNA repair genes (xrcc5, xrcc6) in gastric cancerous and non-cancerous tissue. *J Trace Elem Med Biol*. 2019;55:89–95. doi:10.1016/j.jtemb.2019.06.003
86. Zhu K, Xie V, Huang S. Epigenetic regulation of cancer stem cell and tumorigenesis. *Adv Cancer Res*. 2020;148:1–26. doi:10.1016/bs.acr.2020.05.001
87. Fessler E, Dijkgraaf FE, De Sousa EMF, Medema JP. Cancer stem cell dynamics in tumor progression and metastasis: is the microenvironment to blame? *Cancer Lett*. 2013;341(1):97–104. doi:10.1016/j.canlet.2012.10.015
88. Xiong J, Zhang T, Lan P, Zhang S, Fu L. Insight into the molecular mechanisms of gastric cancer stem cell in drug resistance of gastric cancer. *Cancer Drug Resist*. 2022;5(3):794–813. doi:10.20517/cdr.2022.11
89. Xu M, Gong A, Yang H, et al. Sonic hedgehog-glioma associated oncogene homolog 1 signaling enhances drug resistance in cd44(+)/musashi-1 (+) gastric cancer stem cells. *Cancer Lett*. 2015;369(1):124–133. doi:10.1016/j.canlet.2015.08.005
90. Zhang L, Guo X, Zhang D, et al. Upregulated mir-132 in lgr5(+) gastric cancer stem cell-like cells contributes to cisplatin-resistance via sirt1/creb/abcg2 signaling pathway. *Mol Carcinog*. 2017;56(9):2022–2034. doi:10.1002/mc.22656
91. Ukai S, Honma R, Sakamoto N, et al. Molecular biological analysis of 5-fu-resistant gastric cancer organoids; Khdrbs3 contributes to the attainment of features of cancer stem cell. *Oncogene*. 2020;39(50):7265–7278. doi:10.1038/s41388-020-01492-9
92. Li L, Wei X, Wu B, Xiao Y, Yin M, Yang Q. siRNA-mediated knockdown of id1 disrupts nanog- and oct-4-mediated cancer stem cell-likeness and resistance to chemotherapy in gastric cancer cells. *Oncol Lett*. 2017;13(5):3014–3024. doi:10.3892/ol.2017.5828
93. Huang B, Yan X, Li Y. Cancer stem cell for tumor therapy. *Cancers*. 2021;13(19):4814. doi:10.3390/cancers13194814
94. Zieker D, Buhler S, Ustundag Z, et al. Induction of tumor stem cell differentiation--novel strategy to overcome therapy resistance in gastric cancer. *Langenbecks Arch Surg*. 2013;398(4):603–608. doi:10.1007/s00423-013-1058-5
95. Pang K, Song J, Bai Z, Zhang Z. Mir-15a-5p targets phlpp2 in gastric cancer cells to modulate platinum resistance and is a suitable serum biomarker for oxaliplatin resistance. *Neoplasma*. 2020;67(5):1114–1121. doi:10.4149/neo_2020_190904N861
96. Zhu T, Hu Z, Wang Z, et al. microRNA-301b-3p from mesenchymal stem cells-derived extracellular vesicles inhibits txnip to promote multidrug resistance of gastric cancer cells. *Cell Biol Toxicol*. 2023;39(5):1923–1937. doi:10.1007/s10565-021-09675-0
97. Hang Q, Sun R, Jiang C, Li Y. Notch 1 promotes cisplatin-resistant gastric cancer formation by upregulating lncrna ak022798 expression. *Anticancer Drugs*. 2015;26(6):632–640. doi:10.1097/CAD.0000000000000227
98. Zhong Y, Wang D, Ding Y, Tian G, Jiang B. Circular RNA circ_0032821 contributes to oxaliplatin (oxa) resistance of gastric cancer cells by regulating sox9 via mir-515-5p. *Biotechnol Lett*. 2021;43(2):339–351. doi:10.1007/s10529-020-03036-3
99. Yao W, Guo P, Mu Q, Wang Y. Exosome-derived circ-pvt1 contributes to cisplatin resistance by regulating autophagy, invasion, and apoptosis via mir-30a-5p/yap1 axis in gastric cancer cells. *Cancer Biother Radiopharm*. 2021;36(4):347–359. doi:10.1089/cbr.2020.3578
100. Zheng P, Chen L, Yuan X, et al. Exosomal transfer of tumor-associated macrophage-derived mir-21 confers cisplatin resistance in gastric cancer cells. *J Exp Clin Cancer Res*. 2017;36(1):53. doi:10.1186/s13046-017-0528-y
101. Zhao K, Wang Z, Li X, Liu J, Tian L, Chen J. Exosome-mediated transfer of clic1 contributes to the vincristine-resistance in gastric cancer. *Mol Cell Biochem: An Int J Chem Biol*. 2019;462(1–2):97–105. doi:10.1007/s11010-019-03613-9
102. Ohzawa H, Kimura Y, Saito A, et al. Ratios of miRNAs in peritoneal exosomes are useful biomarkers to predict tumor response to intraperitoneal chemotherapy in patients with peritoneal metastases from gastric cancer. *Ann Surg Oncol*. 2020;27(13):5057–5064. doi:10.1245/s10434-020-09007-2
103. Zheng R, Deng Q, Liu Y, Zhao P. Curcumin inhibits gastric carcinoma cell growth and induces apoptosis by suppressing the wnt/beta-catenin signaling pathway. *Med Sci Monit*. 2017;23:163–171. doi:10.12659/msm.902711
104. Zhou H, Hu X, Li N, et al. Loganetin and 5-fluorouracil synergistically inhibit the carcinogenesis of gastric cancer cells via down-regulation of the wnt/beta-catenin pathway. *J Cell Mol Med*. 2020;24(23):13715–13726. doi:10.1111/jcmm.15932
105. Liu J, Zhu X, Yang D, Li R, Jiang J. Effect of heat treatment on the anticancer activity of houttuynia cordata thumb aerial stem extract in human gastric cancer sgc-7901 cells. *Nutr Cancer*. 2021;73(1):160–168. doi:10.1080/01635581.2020.1737153
106. Liu J, Yuan Q, Guo H, Guan H, Hong Z, Shang D. Deciphering drug resistance in gastric cancer: potential mechanisms and future perspectives. *Biomed Pharmacother*. 2024;173:116310. doi:10.1016/j.biopha.2024.116310
107. Chen X, Xu H, Chen X, et al. First-line camrelizumab (a pd-1 inhibitor) plus apatinib (an vegfr-2 inhibitor) and chemotherapy for advanced gastric cancer (space): a Phase 1 study. *Signal Transduct Target Ther*. 2024;9(1):73. doi:10.1038/s41392-024-01773-9
108. Song X, Lan Y, Zheng X, et al. Targeting drug-tolerant cells: a promising strategy for overcoming acquired drug resistance in cancer cells. *Medcomm*. 2023;4(5):e342. doi:10.1002/mco2.342
109. Kawakami R, Mashima T, Kawata N, et al. Aldh1a3-mtor axis as a therapeutic target for anticancer drug-tolerant persister cells in gastric cancer. *Cancer Sci*. 2020;111(3):962–973. doi:10.1111/cas.14316