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REVIEW

A Review of Research Progress in Multidrug-Resistance Mechanisms in Gastric Cancer

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Tuo Ruan
Weizhen Liu
Kaixiong Tao
Chuanqing Wu

Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

Abstract: Gastric cancer is one of the most common malignant tumors, and it is also one of the leading causes of cancer death worldwide. Because of its insidious symptoms and lack of early dictation screening, many cases of gastric cancer are at late stages which make it more complicated to cure. For these advanced-stage gastric cancers, combination therapy of surgery, chemotherapy, radiotherapy and target therapy would bring more benefit to the patients. However, the drug-resistance to the chemotherapy restricts its effect and might lead to treatment failure. In this review article, we discuss the mechanisms which have been found in recent years of drug resistance in gastric cancer. And we also want to find new approaches to counteract chemotherapy resistance and bring more benefits to the patients.

Keywords: gastric cancer, chemotherapy, resistance

Introduction

Even with the development in medical detection and therapy, the morbidity of gastric cancer still remains to be ranking fourth in all cancers. And it is also the second cause of death due to cancers around the world. East Asian regions, especially China, Japan and Korea, are high-prevalence areas for gastric cancer.[1] In China, gastric cancer is the second most common and deadliest cancer just after lung cancer in 2015. It has been estimated that there are over 700,000 new cases every year, and most of them are in rural area. On the other side, because of its insidious symptoms and lack of early dictation screening, many cases in China are at late stages which bring more difficulties to clinical treatments.[2,3] For advanced-stage gastric cancers, combination therapy of surgery, chemotherapy, radiotherapy and target therapy would bring more benefit to the patients.[4,5] Chemotherapy is one of the main additional methods in treatment, but the rise of drug resistance restricts its effect and might lead to treatment failure.[6–8] In order to solve this problem, we need to study the mechanisms of the chemotherapy resistance and find solutions.

The mechanisms of drug resistance to chemotherapy are complex. According to what we have known, we conclude them into seven aspects as followed: (1) Reduce the effective concentration of intracellular drugs; (2) Change of drugs' targets; (3) Dysfunction of DNA damage repairing; (4) Change of apoptosis and autophagy; (5) Change of tumor micro-environment; (6) Extracellular vesicles and macropinocytosis; (7) MicroRNAs and LncRNAs. Although we have made much progress in studying the molecular mechanisms of the drug resistance, it still lacks applied

Correspondence: Kaixiong Tao; Chuanqing Wu
Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
Email tao_kaixiong@163.com; wucq2014@hust.edu.cn

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technique in detecting and controlling the chemotherapy resistance in clinical practice.[9,10] In this article, we would like to summarize and analyze the research progress in chemotherapy in gastric cancer, and it might lead us to new solutions to this problem.

Reduce the Effective Concentration of Intracellular Drugs

Drug Efflux

The ATP-binding cassette family is a group of the most well-known proteins in constructing transporters in cells.[11–13] These transporters will pump the drugs out of the cells and lead to multi-drug resistance. In these proteins, P-gp, ABCG2 and MRP-1 have been well studied in solid tumors, such as breast cancer, ovarian cancer and gastrointestinal cancers.[14–16] It has been proofed that P-gp is overexpressed in gastric cancer, and would be related to the poor prognosis of the patients.[17,18] The expression of P-gp is also highly related to acquired drug resistance and the risk of relapse after chemotherapy which makes it important in our studies.[16,19]

The regulation pathways of P-gp in regulating drug resistance are diverse. MAPK pathway proteins play important roles as down-stream receptors and in regulating intracellular environment when P-gp is up-regulated in cancer cells.[20] NF-κB could also enhance the expression of P-gp by targeted combining the promoter of P-gp gene to induce multi-drug resistance.[21,22] On the other hand, inhibiting PI3K/AKT pathway could reduce the expression of P-gp and reverse drug resistance.[23] The pathways and molecules which we have mentioned above could serve as targets for us to inhibit drug resistance and provide us with new solutions to this problem.[24,25]

Drug Inactivation

Normal cells could decompose and transform the toxins and their intermediate products to detoxification in order to maintain stable homeostasis. This is also the way that cancer cells decrease the damage from chemotherapeutics.

Glutathione S-transferases (GST) are important in inactivating drugs and induce drug resistance. The main mechanisms are as followed: (1) Catalyze glutathione to combine with electrophilic substrates and prevent reactive oxygen species from causing damage to cell membranes; (2) Up-regulated glutathione and GST will enhance the polarity of drugs to make them inactive; (3) GST could also remove toxic metabolites directly to reduce damage.[26,27] In some researches, we could find that the expression of GST is higher in cancer tissues than normal epithelium.[28] Specifically, it has a strong connection with the drug resistance to platinum.[29,30]

Change of Drugs' Targets

Tumor cells could reduce the level of drugs' targets or enzymes' activity in cells to induce drug resistance. DNA topoisomerase is served as drug targets by many commonly used chemotherapeutics, such as doxorubicin and etoposide. DNA topoisomerase is involved in DNA replication, recombination and repairing process of ribozymes. It is an important part in cell cycle regulation. There are two types of DNA topoisomerase isomers: topoisomerase I (Topo I) and topoisomerase II (Topo II). In gastric cancer, the expression of Topo II is up-regulated, and it has an influence on infiltration depth, histological type and lymph node metastasis. Topo II is also a key factor in inducing resistance to adriamycin and mitomycin C in gastric cancer, and it is correlated to prognosis.[31–34] Research has noticed that down-regulating the expression of Topo II would strengthen the resistance to adriamycin.[35] This would lay the foundation for us to solve this kind of chemotherapy resistance.

With the development of new drugs and therapies, molecule-targeted therapy has become a hotspot in recent years for its higher efficiency and less side-effects.[36,37] In gastrointestinal cancers, imatinib has been widely used in curing GIST and has made great progress. It targets at tyrosine kinase to inhibit PDGF receptors, SCF and c-Kit receptors. While in clinical practice, we have found that the mutation of Kit and BRAF gene would lead to drug resistance to imatinib.[38,39] This situation demands us to study in the next generation of targeted drugs and make individual treatment more specific.

Dysfunction of DNA Damage Repairing

In normal cells, DNA damage repairing is activated when they have physical, chemical or biological damages in order to stabilize chromatin. However, when the repairing system is dysfunctional, it would lead to oncogenesis.[40,41] Chemotherapy utilizes DNA damage and cytotoxicity as an approach to kill cancer cells, especially for platinum drugs. Platinum inhibits DNA transcription and replication, and it might cause DNA cleavage which makes DNA damage repairing activation a key factor in drug resistance to platinum.[42,43]

Nucleotide excision repair (NER) is an important pathway to repair the damage caused by chemotherapy drugs through identification, resection and reconstruction of damaged DNA. And this progress is composed of dozens of proteins.[44,45] While DNA mismatch repair genes (MMR), such as MLH1, also play a role in the development of gastric cancer and inducing drug resistance.[46] These pathways could offer us a road to reverse drug resistance to platinum and bring benefits to the patients.

Change of Apoptosis and Autophagy

Dysfunction of Apoptosis Pathways

There are two classical apoptosis pathways in human: (1) Endogenous pathway mediated by mitochondria; (2) Exogenous pathways mediated by tumor necrosis factor (TNF) receptors.[47]

The Bcl-2 protein family contains a variety of apoptosis-related proteins, such as Bax, Bad and Bid which induce apoptosis, and Bcl-2, Bcl-xl which inhibit the progress. These proteins interact with each other in order to maintain a relatively stable state for cells. When this balance is broken, it would likely lead to carcinogenesis and have resistance effects on chemotherapeutics which aim at inducing cell apoptosis.[48,49] In gastric cancer, studies have shown that the over-expression of Bcl-2 is highly related to drug resistance, and it is also an important influence factor in prognosis.[50,51] Bax, which is promoting apoptosis, has been confirmed to be used in predicting the patients' response to chemotherapy.[52] Upregulating the expression of Bax could help to promote sensitivity to chemotherapy in cancer cells by releasing cytochrome C from mitochondria.[53] In addition, other members in the Bcl-2 family, such as Bcl-xL and Bak, also have been proved to be playing relevant roles in drug resistance.[54,55] These make Bcl-2 family critical in gastric cancer development and chemotherapy resistance. They would hopefully be a breakthrough point in our research.

Tumor necrosis factor (TNF) family proteins, such as NFRS-1, Fas, DR4 and DR5, are also important in cell apoptosis regulation. Studies have shown that Fas could induce cell apoptosis to eliminate tumor cells by combining with FasL, while the increase in soluble Fas will inhibit apoptosis.[56,57] A recent study has found that the expression of TNF-related apoptosis-inducing ligand (TRAIL) had a negative correlation with multidrug resistance-associated protein P-gp, and P-gp could achieve multi-drug resistance by regulating the expression of TRAIL and its mediated apoptosis pathway.[58]

P53 is one of the most popular tumor suppressor genes in our studies, and it has multiple functions in cell cycle regulation, DNA repairing and cell apoptosis. Researches have shown that p53 mutation is an important influence factor in gastric cancer development, and high expression of p53 gene is associated with poor prognosis.[59,60] At the same time, p53 also takes part in gastric cancer drug resistance. We could find that patients with mutant p53 have a better response to chemotherapy.[61] And recent studies suggest that rAd-p53 could induce cell apoptosis in gastric cancer cells, and p53 could reverse cisplatin resistance by regulating the AKT signaling pathway and the expression of Bax.[62,63]

PI3K/AKT pathway is crucial in cell growth and proliferation. Abnormal activation of the PI3K/AKT pathway has been reported to be one of the important mechanisms of inducing drug resistance in tumor cells.[64,65] And further studies have showed that some chemotherapeutics would activate the PI3K/AKT pathway which resulted in acquired drug resistance.[66,67] So far, the mechanisms of the PI3K/AKT pathway have not been fully understood. And the abnormal activation of the PI3K/AKT pathway in tumor cells might be via PI3K catalytic subunit of alpha (PIK3CA) mutation or loss of PTEN gene function.[68,69] NF-κB could serve as a down-stream targeted protein and take part in inducing drug resistance.[70] P-gp, Bcl-2 and Bax could also be regulated by phosphorylated AKT.[24] At the same time, how to make use of the PI3K/AKT pathway in clinical treatment is also on the schedule. Now, research has proved that the AKT inhibitor could reverse the drug resistance of gastric cancer cells.[71] Further validation and application researches have been carried out and would get promising results for clinical works.[72]

Change of Autophagy Pathways

Autophagy is a cellular survival mechanism which is a highly conserved cellular process to degrade cytoplasmic materials and recycle to maintain energy homeostasis. And it could be induced by cancer therapy, among other stresses, and frequently contributes to cancer cell survival.[73–75] Autophagy can also be classified as macro-autophagy, micro-autophagy, and chaperone-mediated autophagy.

Molecular mechanisms of autophagy could be divided into initiation, nucleation and elongation of autophagosome, fusion of autophagosome with the lysosome, and degradation of sequestered material. Autophagy is

constitutively activated in cancer cells through the deregulation of PI3K/Akt/mTOR molecular axis and AMP-activated protein kinase (AMPK) signal transduction, which contributes to the metabolic reprogramming of cancer cells.[76–78]

A large amount of cancer therapies has been shown to induce autophagy, while many of them indicate that autophagy turns out to promote tumor cell survival and contribute to therapy resistance.[79,80] Some studies have also shown that autophagy-related proteins, such as Beclin 1 (BECN1), microtubule-associated protein1 light chain 3 (MAP1-LC3), and p62/sequestosome 1 (SQSTM1) have an important prognostic value in gastric cancer, and act as a protective mechanism for tumor cells in chemotherapy, promoting drug resistance as well.[81–83] The therapeutic induction of autophagy is frequently attributed to reduced mTOR activity leading to autophagy de-repression, and this is most obvious with therapies targeted at inhibiting PI3K, AKT or indeed mTOR itself. In addition, autophagy is induced by conventional genotoxic agents, such as radiation or cisplatin, as a result of DNA damage-induced p53 activity. However, the role of p53 in these responses is complicated. Depending on the context, it can also inhibit autophagy.[84,85] As there are a growing number of studies in autophagy and its cytoprotective effect, there might be a chance to help cancer therapeutic approaches with agents that inhibit autophagy.[86,87]

Change of Micro-Environment

There is extracellular matrix, a variety of trace elements, immune cells and other substances in tumor's microenvironment. These substances have multiple effects on proliferation, invasion, metastasis and multi-drug resistance.[88–90]

Extracellular Matrix

Extracellular matrix is a complex network containing multifunctional molecules and has an important influence on tumor development. Laminin and collagen IV are important parts of the basement membrane in the gastric cancer's extracellular matrix.[91] And the overexpression of laminin would enhance gastric cancer cells' resistance to vincristine and adriamycin via regulating MGr1-Ag/37LRP.[92] This phenomenon also indicates that cell adhesion ability is associated with the chemo-resistant phenotype of gastric cancer cells, which makes it has a chance to be considered as a reference target to detect drug resistance. The mechanisms of how laminin induced drug resistance in gastric cancer are varied, including regulating the expression of multiple drug resistance-related proteins such as P-gp, and regulating apoptosis-related proteins Bcl-2 and Bax to inhibit drug-mediated apoptosis and multiple signaling pathways (PI3K/AKT and MAPK/ERK).[92,93] Besides these, the high expressions of metalloproteinases inducer HMGB1 are also related to drug resistance.[94,95] Thus, there are still more details needed to be explored between the extracellular matrix and tumor drug-resistance mechanism which will bring more benefits to clinical treatment.

Cytokines and Growth Factors

The cytokines and growth factors in tumor microenvironment are involved in the activation of a variety of signaling pathways and play a key role in chemoresistance. Many cytokines and growth factors have been confirmed to act as independent factors that influence prognosis in gastric cancer patients under chemotherapy treatment.[96] Interleukin family is a major part of cytokines that have been well studied. IL-6 could lead to acquired drug resistance to trastuzumab in gastric cancer cells via activation of the STAT3 signaling pathway.[97] IL-33 could cause resistance to platinum through the JNK signaling pathway.[98] And IL-24 has also been proved to be involved in regulating multi-drug resistance.[99]

Anoxia

Anoxia is an important biological characteristic in tumorigenesis and is also one of the mechanisms in drug resistance. HIF-1α is critical in cells' response to hypoxia, and the over-expression of HIF-1α has been confirmed to be related to poor prognosis in gastric cancer in multiple studies which makes it an independent factor predicting prognosis.[100–102] Some studies have showed that HIF-1α could regulate drug resistance by regulating the expression of p53, NF-κB, Bcl-2 and serving as the down-stream target of PI3K/AKT and MAPK/ERK signaling pathways.[103–106] HIF-1α has played a significant role in inducing drug resistance in gastric cancer, while the mechanisms are still needed to be explored.[103]

Extracellular Vesicles and Micropinocytosis

Extracellular vesicles (EVs) are secreted by nearly almost cells and released to the extracellular space. EVs could be divided into three different subgroups according to their size: exosomes (30–100 nm), micro-vesicles (MVs, 100–1000

nm), and apoptotic bodies (1000–5000 nm). While exosomes are small membrane nanovesicles which constituted through the intraluminal budding of the late endosomal membrane and are secreted from the plasma membrane.[107–109] Recently, the finding that paclitaxel-resistant gastric cancer cell line (MGC-803R) cell-derived exosomes could be taken up by paclitaxel-sensitive MGC-803 (MGC-803S) cells has been reported. Furthermore, the exosomal miR-155-5p from MGC-803R cells can join in directly inhibiting GATA binding protein 3 (GATA3) and tumor protein p53-inducible nuclear protein 1 (TP53INP1) to induce chemoresistant phenotypes in the sensitive cells which uptake the exosomes.[110,111] In addition, exosomal miR-21 can be directly transferred from macrophages to gastric cancer cells to obtain the chemotherapy resistance, and inhibit cell apoptosis and activate the PI3K/AKT pathway by regulating PTEN.[112]

Macropinocytosis has been known as a primary method for the cellular intake of fluid-phase and membrane-bound bulk cargo. And recent researches show that direct roles for macropinocytosis within tumorigenesis.[113] Uptake of nutrients in the tumor microenvironment by macropinocytosis has recently been named as an emerging hallmark of cancer metabolism.[114,115] In lung cancer cell line A549, it has been demonstrated the extracellular ATP was internalized by macropinocytosis and induced intracellular ATP increase and drug resistance.[116] In addition, there are several researches associated with macropinocytosis and drug resistance in pancreatic cancer and breast cancer.[117,118] The mechanisms and effects of micropinocytosis in gastric cancer need further study, and it may lead to a new way to solve the multi-drug resistance in gastric cancer.

MicroRNAs and LncRNAs in Drug Resistance in Gastric Cancer

With the development of research in drug resistance, new research objects are introduced into this study. MicroRNAs are noncoding single-stranded RNA molecules which contain 18 to 22 nucleotides encoded by endogenous genes. They are involved in regulating gene expression and have extensive application prospects in tumor researches,[119] while lncRNAs refer to nucleotides long-chain non-coding RNA which have more than 200 nucleotides. And recent studies reveal that they are involved in cell cycle regulation, epigenetic regulation and many other aspects which make them become a focus of current researches. LncRNAs also play an important role in tumorigenesis and might be the breakthrough point.[120,121] Now, we will, respectively, introduce the two types of molecules in the research of gastric cancer's drug-resistance briefly.

MicroRNAs in Drug Resistance of Gastric Cancer

MicroRNAs have been extensively studied in recent years; their important roles in numerous biological behaviors begin to be revealed. A growing number of studies prove that microRNAs are significant in regulating drug transporters, transcription factors and nuclear receptors which may lead us to a new approach in drug-resistant treatment.[122] In the study of the drug resistance in gastric cancer, microRNAs are also involved in several classic signaling pathways.

Bcl-2-related apoptosis pathway is important in regulating drug resistance in gastric cancer, and the current researches have shown that a variety of microRNAs are involved in regulating this pathway. MiR-503 and miR-143 can regulate the expression of IGF1R and Bcl-2 to mediate gastric cancer cells' resistance to cisplatin.[123,124] The study of miR-200 BC/429 finds that high expression of miR-200 BC/429 will strengthen sensitivity of SGC7901/vincristine (VCR) cell line to cisplatin (CDDP), etoposide (VP-16) and adriamycin (ADR), while it is not suitable for 5-fluorouracil. And when these cells were transfected with miR-200 BC/429 inhibitor, their resistance to cisplatin, etoposide and adriamycin was enhanced. Through the luciferase assay, the Bcl-2 3′-UTR reporters were detected in resistant SGC7901 cells which suggested that Bcl-2 was a target gene of the miR-200bc/429 cluster.[125]

PI3K/AKT signaling pathway is another important signaling pathway in drug-resistance mechanisms, while microRNAs are also involved in it. MiR-21 is detected highly expressed in SGC7901/cisplatin (CDDP) resistant cell line. Further experiments confirm that when the cells are induced with over-expression of miR-21, cell apoptosis caused by cisplatin injury would significantly reduce. On the other hand, decreasing the expression of miR-21 increases the anti-proliferative effects and CDDP-related apoptosis. It is also been found that miR-21 regulates cisplatin resistance via down-regulating the expression of PTEN and activation of the PI3K/AKT signaling pathway. This also provides us with a new method in handling the cisplatin resistance in gastric cancer via PI3K/PTEN/AKT

pathway.[126] Besides, miR-21 could also regulate trastuzumab's efficiency in addition to chemotherapy in patients with HER2-positive gastric cancer. Over-expressed miR-21 would inhibit gastric cancer cell apoptosis caused by the drugs while inhibiting its expression would help with the therapy.[127,128] This result would make microRNAs an important aid in individualized medicine.

For microRNAs involve in a wide variety of drug-resistance mechanism in gastric cancer, further researches are required to conduct.[129,130] Although there is a long road for microRNAs from being applied to the treatment, they still introduce us with a new way for our future cancer treatment. New treatments based on microRNAs will come out in the near future promisingly.

LncRNAs in Drug Resistance of Gastric Cancer

In the study of gastric cancer, a variety of abnormal-expressed lncRNAs have been proved to be critical in tumorigenesis, metastasis and drug resistance. PVT1, a lncRNA which is associated with gastric cancer, is closely related with the development and MDR in gastric cancer. Recent researches show that PVT-1 is highly expressed in gastric cancer tissues of cisplatin-resistant patients and SGC7901/DDP cells. In addition, PVT1 is also a risk factor in lymph nodes metastasis. These features make PVT1 have the potential to be the new biomarkers for the evaluation of patients with gastric cancer.[131,132] And in the prescription of drug resistance in gastric cancer, up-regulating PVT1's expression would raise the expression of p-glycoprotein, MRP, mTOR and HIF-1α to induce multidrug-
resistance, while inhibiting PVT1's expression would reverse cell resistance to cisplatin.[133,134] Other studies have shown that down-regulating the expression of LEIGC in gastric cancer cells could enhance the resistance to 5-fluorouracil via regulating the EMT process, which suggested LEIGC could be a suppressor lncRNA in gastric cancer.[135] Further studies have found that the target site of lncRNA MRUL is close to p-glycoprotein, and the expression of MRUL is higher in drug-resistance cells. For p-glycoprotein is one of the important proteins in inducing multidrug resistance, patients with high expression of MRUL show poor reactivity of chemotherapy drugs in clinical practice. And another study reveals that MRUL induces resistance to adriamycin by regulating the expression of ABCB1 in gastric cancer.[136]

New lncRNAs are also added to some common molecular mechanism and signaling pathway due to the recent studies, such as Notch 1 could increase lncRNA AK022798 expression to induce resistance to cisplatin in gastric cancer.[137] LncRNA HOTAIR could also activate the PI3K/AKT pathway and regulate the expression of p-glycoprotein through miR-216.[138] On the other hand, the connection between lncRNAs and microRNAs has been revealed, such as lncRNA UCA1 could enhance drug resistance by down-regulating miR-27b.[139] With the deepening of the researches, lncRNAs could play a more active role in gastric cancer drug-resistance treatment.

Discussion

The preferred treatment for advanced-stage gastric cancer is still surgical operation.[140,141] However, for patients who have no chance to get surgical treatment, the ultimate goal of comprehensive treatment is to prolong survival and improve the quality of life. The development and progress of novel chemotherapy, targeted drugs, immunotherapy will provide new opportunities for the comprehensive treatment of gastric cancer. We could bring better clinical benefit to patients by carrying out a more comprehensive and personalized diagnosis and treatment strategy. Meanwhile, drug resistance is still one of the major obstacles in gastric cancer treatments. Although there are many mechanisms that have been revealed above, the clinical application is still limited.

The networks of drug-resistance-related pathways are complicated, and many proteins and molecules are involved (Figure 1). It might be hard to distinguish them apart. But the main goal of improving the therapy by enhancing the efficiency of the drugs is similar.

As we have discussed above, the regulation of certain miRNA or lncRNA expressions could participate in improving the response of GC cell lines to chemotherapy and significantly enhance the antitumor properties of specific drugs. It could be helpful in developing personalized therapies, as well as establishing novel therapeutic strategies to reverse the resistance of tumors in combination with chemotherapeutic agents. And macropinocytosis could be used as a new target for therapy and might help with transfer the drug into the cells. Despite these hypotheses, there are many other ways we could try in this field.

In conclusion, there are more studies have been carried out to reveal the mechanisms of drug resistance in gastric cancer, the related pathways and molecules above are likely to help us solve this problem in future. For drug

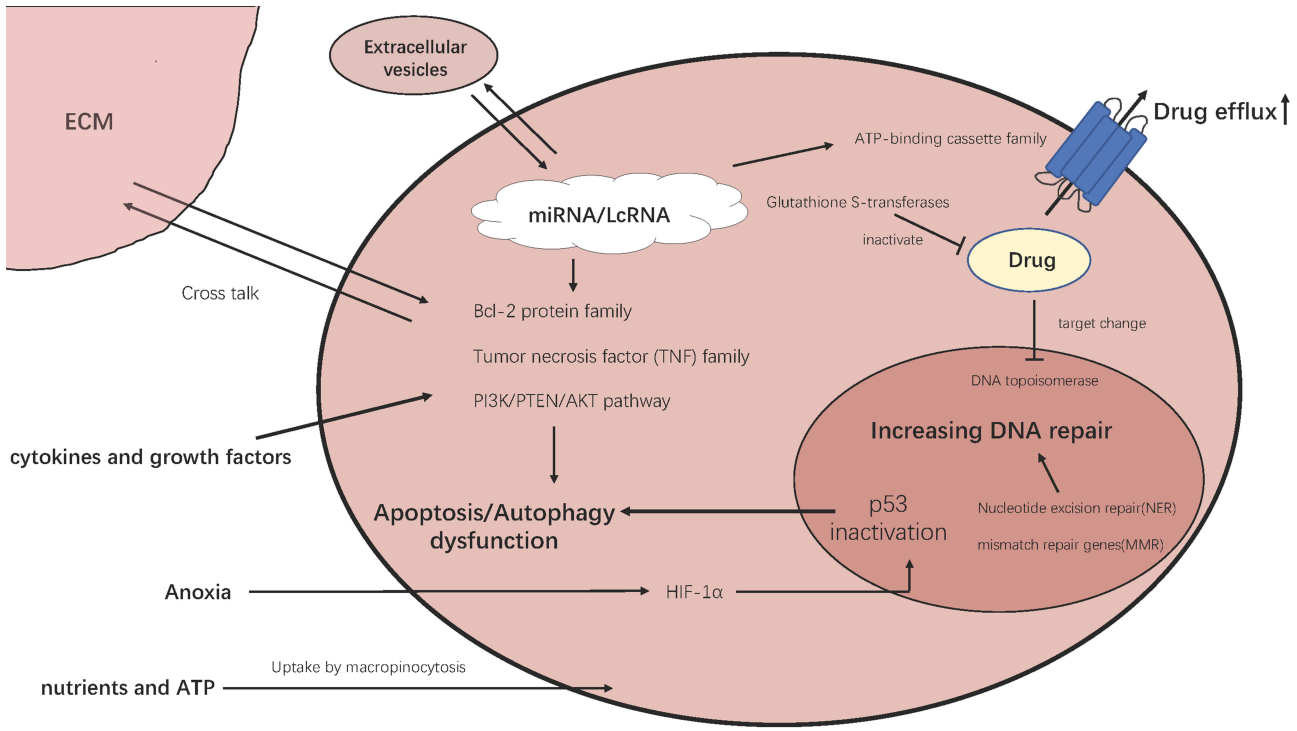

Figure 1 The summary of mechanisms of drug resistance in gastric cancer.

resistance is caused by multiple factors, it makes our research more complicated and brings a challenge in clinical application. However, we should believe that with the development of our technology, the situation will be improved and the patients will get benefit.

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Disclosure

The authors declare no competing interests.

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