World Journal of Gastrointestinal Oncology

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DOI: 10.4251/wjgo.v8.i9.673

World J Gastrointest Oncol 2016 September 15; 8(9): 673-681
ISSN 1948-5204 (online)
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REVIEW

Molecular mechanisms of chemoresistance in gastric cancer

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Author contributions: Shi WJ and Gao JB contributed equally to this work.

Supported by National Natural Science Foundation of China, No. 81572411.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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Manuscript source: Invited manuscript

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Received: March 27, 2016
Peer-review started: March 28, 2016
First decision: May 23, 2016
Revised: June 7, 2016
Accepted: June 27, 2016
Article in press: June 29, 2016
Published online: September 15, 2016

Abstract

Gastric cancer is the fourth most common cancer and the second leading cause of cancer deaths worldwide. Chemotherapy is one of the major treatments for gastric cancer, but drug resistance limits the effectiveness of chemotherapy, which results in treatment failure. Resistance to chemotherapy can be present intrinsically before the administration of chemotherapy or it can develop during chemotherapy. The mechanisms of chemotherapy resistance in gastric cancer are complex and multifactorial. A variety of factors have been demonstrated to be involved in chemoresistance, including the reduced intracellular concentrations of drugs, alterations in drug targets, the dysregulation of cell survival and death signaling pathways, and interactions between cancer cells and the tumor microenvironment. This review focuses on the molecular mechanisms of chemoresistance in gastric cancer and on recent studies that have sought to overcome the underlying mechanisms of chemoresistance.

Key words: Drug resistance; Gastric cancer; Chemotherapy

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Core tip: Although chemotherapy remains one of the primary therapeutic modalities used in the treatment of gastric cancer, chemoresistance limits the effectiveness of chemotherapy and results in treatment failure. The elucidation of the mechanisms of drug resistance will be very helpful for the prediction of sensitivity to chemotherapy and the reversal of drug resistance to improve therapeutic efficacy. The mechanisms of drug resistance have been broadly investigated in recent years. In this review, we summarize the molecular mechanisms of chemoresistance in gastric cancer and discuss the progress in the reversal of drug resistance.

Shi WJ, Gao JB. Molecular mechanisms of chemoresistance in gastric cancer. *World J Gastrointest Oncol* 2016; 8(9): 673-681 Available from: URL: http://www.wjgnet.com/1948-5204/full/v8/i9/673.htm DOI: http://dx.doi.org/10.4251/wjgo.v8.i9.673

INTRODUCTION

Gastric cancer is one of most common malignant tumors. It currently ranks as the fourth most common cancer and is the second leading cause of cancer deaths worldwide. The incidence of gastric cancer varies greatly in different regions, and over 70% of new cases and deaths occur in developing countries. The highest incidence rates are observed in Eastern Asia, Eastern Europe, and South America, whereas the lowest rates are observed in North America and most parts of Africa[1].

Although the incidence of gastric cancer has declined due to improved living standards, a reduction in chronic *H. pylori* infection and increased screening activities, the overall outcome has not significantly improved over the last few decades. The treatment outcomes for gastric cancer are determined by the stage of the tumor at presentation and the condition of the patients. Surgery is the only potentially curative treatment for gastric cancer. The five-year overall survival rate after surgery varies from 70%-95% in early stage patients to 20%-30% in advanced-stage patients. Moreover, more than two-thirds of patients have unresectable disease when they are diagnosed[2]. Therefore, chemotherapy is used to relieve symptoms in patients with unresectable tumors and to reduce the risk of recurrence and metastasis in patients with localized disease after surgery. Perioperative chemotherapy can improve the 5-year survival rate from 23% to 36.3% among patients with resectable adenocarcinoma of the stomach compared with surgery alone[3]. In addition, chemotherapy has shown only a modest benefit in patients with metastatic disease with an average survival of approximately ten months[4,5].

Although chemotherapy plays an important role in the treatment of both local and metastatic gastric cancer, the efficacy of chemotherapy is limited by chemoresistance. Chemotherapeutic resistance, whether intrinsic or acquired, is a complex and multifactorial phenomenon that is associated with tumor cells as well as with the tumor microenvironment[6]. With the development of modern biological techniques, the mechanisms of chemoresistance have been broadly investigated in recent years. This review focuses on the molecular mechanisms of chemoresistance in gastric cancer and on recent studies that have sought to overcome the underlying mechanisms of chemoresistance.

REDUCED INTRACELLULAR CONCENTRATION OF DRUGS

Drug efflux

The ATP-binding cassette (ABC) transporter family has been shown to be associated with chemoresistance. These transmembrane proteins can reduce the intracellular concentrations of drugs *via* an increase in the efflux of drugs and the redistribution of drugs away from the site of action. This family of proteins is composed of 49 members that are divided into 7 subclasses (ABCA-ABCG). ABCB1, also known as P-glycoprotein and MDR1, was the first ABC transporter to be identified and has been studied extensively. The overexpression of ABCB1 has been found in human gastric cancer cell lines and in clinical gastric cancer tissues[7-9]. The association between ABCB1 expression and the clinicopathological characteristics of patients with gastric cancer is not fully understood. According to one study, ABCB1 expression was less frequent in locally advanced tumors and was absent in primary tumors where distant metastases were also present[8]. In another study, ABCB1 expression was also associated with well and moderately differentiated tumors and intestinal-type tumors, but it did not indicate poor prognosis of gastric cancer patients treated with 5-fluorouracil (5-FU) and doxorubicin-based adjuvant chemotherapy[10]. Recent reports have suggested that the expression of ABCB1 is related to poor prognosis in gastric cancer patients[9,11]. Further studies have indicated that the expression of ABCB1 is associated with chemoresistance in patients with gastric cancer, as its presence in tumor cells may be an indicator of a lack of sensitivity to chemotherapy[12-15]. The expression of ABCB1, which results in acquired chemoresistance, can be induced by chemotherapy. The expression rate of ABCB1 increased from 27.8% to 37.5% after the administration of adriamycin-based chemotherapy. ABCB1 expression after chemotherapy has been correlated with a higher rate of systemic recurrence[16]. ABCB1 has been demonstrated to affect intrinsic and acquired resistance of gastric cancer cells to chemotherapeutic agents. Blocking the expression of ABCB1 can reverse multidrug resistance in human gastric carcinoma cells[17,18]. Other ABC transmembrane proteins, such as ABCC1, which is also known as multidrug resistance-associated protein, are also associated with multidrug resistance in gastric cancer[9,19,20].

The expression of ABCB1 is regulated by a variety of factors. NF-kappa B is a transcriptional factor that can bind to gene promoters or enhancer sites to promote the transcription of those genes. Bentires-Alj *et al*[21] identified a consensus NF-kappa B binding site in the first intron of the human *ABCB1* gene and demonstrated that NF-kappa B can bind to this intronic site and activate reporter gene transcription. Gu *et al*[22] demonstrated that upon paclitaxel stimulation, cyclooxygenase-2 induced the expression of ABCB1 in gastric cancer cells *via* the NF-kappa B pathway. Another study found a positive association between phosphorylated AKT (p-AKT) and ABCB1 expression in both gastric cancer tissues and gastric cancer cell lines. Moreover, it was shown that the expression of ABCB1 was reduced by the inhibition of the phosphatidylinositol-3 kinase (PI3K)/AKT pathway in SGC7901/ADR cells. Ubiquitin ligase Cbl-b can also down-regulate the expression of ABCB1 through the suppression of the PI3K/AKT signaling pathway. These findings indicated that the PI3K/AKT pathway might regulate the expression of ABCB1 and may be correlated with chemoresistance[23]. Recently, some studies have demonstrated that microRNAs play an important role

in chemoresistance *via* the regulation of the expression of ABCB1. miR-508-5p can repress the expression of ABCB1 by targeting the 3'UTR of ABCB1[24]. miR-106a and miR-27a, through the up-regulation of ABCB1 expression, are also involved in chemoresistance in gastric cancer[25,26]. In addition, the long non-coding RNA PVT1 has been shown to increase the expression of multidrug resistance-related genes [*ABCB1*, *ABCC1*, *mTOR* and Hypoxia-inducible factor-1alpha (HIF-1α)], which in turn results in the development of chemoresistance in gastric cancer[27].

Drug inactivation

Glutathione *S*-transferases (GSTs) are a family of phase Ⅱ detoxification enzymes that catalyze the conjugation of glutathione (GSH) to a broad variety of hydrophobic and electrophilic compounds. GSTs are involved in chemoresistance because they inactivate drugs. The expression of glutathione *S*-transferase-pi (GST-pi) has been found in both gastric cancers and in normal gastric mucosa, but the total GST enzyme activity and the absolute amounts of GST-pi protein were significantly higher in tumors compared with those of matched normal mucosa[28]. Differences were found in the GSH and GST parameters between responsive and progressive patients with gastric cancer who were treated with chemotherapy, which suggests a role for the GSH/GST system in the susceptibility of gastric tumor cells to chemotherapy[29]. The overexpression of GST-pi has been found to be significantly related to the sensitivity of gastric cancer to cisplatin[30]. It was reported that GST-alpha is correlated with cisplatin resistance in gastric cancer, and the quantification of GST-alpha can be used to predict the clinical effects of cisplatin in patients with gastric cancer[31]. Lastly, 3β-acetyl tormentic acid has been shown to sensitize multidrug-resistant cells to antineoplastic drugs through the modulation of intracellular levels of GSH and GST activity[32].

Reduced prodrug activation

The reduced activation of prodrugs may decrease the intracellular concentrations of the corresponding active drugs, which results in the reduction of chemotherapeutic efficacy. 5-FU is a common chemotherapy drug whose activation involves thymidine phosphorylase, uridine phosphorylase and orotate phosphoribosyl transferase. Lower expression or impaired activity of these enzymes has been associated with chemoresistance to 5-FU in gastric cancer[33-35].

ALTERATIONS IN DRUG TARGETS

DNA topoisomerases are a class of nuclear enzymes that modulate DNA topology during chromosomal transactions, such as gene transcription and DNA replication, recombination and repair. Topoisomerases are targets of various chemotherapeutic agents such as doxorubicin, etoposide, mitoxantrone and irinotecan. Alterations in topoisomerases could affect a patient's response to chemotherapy as well as resistance. A series of studies revealed higher Topo-Ⅱ expression in gastric carcinomas compared with normal gastric mucosa, and this increased expression was correlated with clinicopathological parameters such as tumor location, histological type, infiltration depth, distant metastases and tumor stage[36-39]. A reduction in Topo-Ⅱ expression was also found to contribute to the resistance of human gastric cancer cells to adriamycin and other topo Ⅱ-targeted drugs *in vitro*[40]. Furthermore, Topo-Ⅱ expression has been negatively correlated with hydroxycamptothecin, adriamycin and mitomycin C resistance in gastric cancer tissues[41].

Paclitaxel is an anti-microtubule drug that interferes with tubulin and that stabilizes microtubule composition, normal spindle assembly and cell division, which all result in cancer cell death. The clinical effectiveness of paclitaxel and the expression of the microtubule-associated protein tau have therefore been investigated[42]. Among 20 cases of inoperable or noncurative, resected gastric cancer, 14 demonstrated positive tau expression while 6 were negative for tau expression. All six tau-negative cases showed a favorable response to paclitaxel, whereas 12 of the 14 tau-positive cases showed progressive disease or no change after paclitaxel administration. These results indicated that tau-negativity may be used to select gastric cancer patients who will respond favorably to paclitaxel treatment. Another study demonstrated that the sensitivity of gastric cancer patients to paclitaxel treatment was inversely correlated with the expression of class Ⅲ b-tubulin and the microtubule-associated protein tau[43]. Additionally, low miR-34c-5p expression and high microtubule-associated protein tau protein expression were found in paclitaxel-resistant gastric cancer samples. The overexpression of miR-34c-5p causes a significant down-regulation of tau protein expression, which leads to an increase in the chemosensitivity of paclitaxel-resistant gastric cancer cells. Therefore, the modulation of microtubule-associated proteins might play an important role in the chemoresistance of gastric cancer cells to paclitaxel[44].

DYSREGULATION OF CELL SURVIVAL AND DEATH

Chemotherapeutic drugs cause DNA damage and induce cell death, and escape from cell death is one of the mechanisms of chemoresistance. The promotion of cell survival and resistance to apoptosis are both hallmarks of cancer cells. Accumulating evidence has shown that the dysregulation of cell survival and death is involved in the resistance of cancer cells to chemotherapeutic drugs.

BCL-2 family members

The BCL-2 protein family comprises a group of apoptosis regulators. These proteins can be divided into the following three subfamilies: The anti-apoptotic subfamily,

which contains the BCL-2, BCL-xL, BCL-w, MCL-1, BFL1/A-1, and BCL-B proteins; the pro-apoptotic subfamily, which contains the BAK, BAX, and BOK proteins; and the BH3-only protein subfamily, which contains the pro-apoptotic BIM, BID, BIK, BAD, BMF, HRK, PUMA, and NOXA proteins[45]. Interactions among the BCL-2 protein family members within the mitochondrial outer membrane control cellular commitment to apoptosis[46]. The role of the BCL-2 family of proteins in chemoresistance has been studied extensively.

Studies have demonstrated that the overexpression of BCL-2 is associated with chemoresistance to cytotoxic chemotherapeutic agents in patients with gastric cancer[47,48]. The silencing of BCL-2 increased cell apoptosis and decreased resistance to 5-FU in gastric adenocarcinoma cells[49]. This suggested that the modulation of BCL-2 expression could affect chemosensitivity in gastric cancer. A recent study showed that Rho GDP dissociation inhibitor 2 rendered gastric cancer cells resistant to cisplatin *via* the up-regulation of BCL-2 expression[50]. In addition, microRNAs are small, endogenous noncoding RNAs that negatively regulate gene expression at the posttranscriptional level. Several microRNAs, such as miR-204, miR-181b, miR-15b and miR-16, were found to up-regulate the expression of BCL-2, which resulted in multidrug resistance in human gastric cancer cells[51-53].

The pro-apoptotic protein BAX has been demonstrated to predict clinical responsiveness to chemotherapy in patients with gastric cancer[54]. Increased BAX expression has also been shown to sensitize KATO Ⅲ cells to chemotherapeutic agent-induced apoptosis through the enhancement of the release of cytochrome c from mitochondria[55]. Our studies showed that interferon regulatory factor 1 enhanced the chemosensitivity of gastric cancer cells to 5-FU through the induction of PUMA-mediated apoptosis[56,57]. Other BCL-2 family members (BCL-xL, BAK, MCL-1) have also been demonstrated to function in the regulation of chemotherapy-induced apoptosis[58,59]. This indicated that proteins in the BCL-2 family, through interactions among its members, play a pivotal role in the determination of cell fate following chemotherapy.

p53

The *p53* tumor suppressor gene plays an important role in various processes, including cell cycle regulation, DNA repair and apoptosis. In one study, mutations in the *p53* gene were found in 0%–77% of gastric carcinomas[60]. Moreover, *p53* alterations including a high frequency of *p53* mutations, loss of heterozygosity, overexpression of the p53 protein, and consequently, the loss of p53 function, are early events in gastric cancers; they are also important biomarkers that are used to determine prognosis and treatment response[61]. Although the relationship between p53 and chemoresistance in gastric cancer has been studied for many years, the results are not consistent. Recently, a meta-analysis was performed to expound the relationship between p53 status and the response to chemotherapy[62]. Thirteen published studies were eligible, including 564 cases, which were identified and analyzed. The results showed that p53 positive status (*i.e.*, high expression of p53 protein and/or a mutant *p53* gene) was associated with an improved response in patients with gastric cancer who received chemotherapy. This indicated that p53 status might be a useful predictive biomarker for response to chemotherapy in gastric cancer. A later study showed that rAd-p53 enhanced the sensitivity of gastric cancer cells to chemotherapy *via* the promotion of apoptosis[63]. The restoration of p53 was able to overcome cisplatin resistance in gastric cancer through the inhibition of AKT as well as through the induction of BAX[64].

PI3K/AKT pathway

The PI3K/AKT pathway is a vital regulator of cell growth, proliferation and survival. The stimulation of receptor tyrosine kinases or G-coupled proteins activates PI3K, which in turn activates AKT; the phosphorylation of AKT is required for the complete activation of AKT. Activated AKT then phosphorylates various substrates so that it can exert its functions in cell proliferation, growth, anti-apoptosis and cell cycle progression. Aberrant activation of the PI3K/AKT pathway, which is believed to play an important role in resistance to chemotherapy, has been reported in human malignancies including gastric cancer.

Mutations in PIK3CA, which lead to increased PI3K activity, have been reported in gastric cancer[65,66]. The expression of AKT and p-AKT was found in 74% and 78% of gastric carcinomas, respectively[67]. It has been reported that the expression of p-AKT is correlated with depth of infiltration of the tumor, number of infiltrated lymph nodes, and overall survival[68]. Moreover, several studies have shown that activated AKT is associated with increased resistance to multiple chemotherapeutic agents including 5-FU, adriamycin, mitomycin C and cis-platinum[69,70]. Further studies demonstrated that chemotherapeutic reagents can induce activation of the PI3K/AKT signaling pathway, which results in acquired chemoresistance in gastric cancer cells[71,72]. In addition, in one study, the overexpression of AKT decreased the chemosensitivity of gastric cancer cells to cisplatin, whereas the down-regulation of AKT reversed the resistant phenotype of gastric cancer cells *in vitro* and *in vivo*[73,74].

Studies have reported that the aberrant activation of the PI3K/AKT pathway can be induced by various factors, including mutations in PIK3CA[65], loss of PTEN function[69], mutations in AKT isoforms[75], and upstream activation of other growth pathways (*e.g.,* EGFR signaling pathway)[76]. Although the PI3K/AKT pathway plays an important role in chemoresistance, the mechanism of PI3K/AKT activation that results in chemoresistance is not fully understood. It has been reported that NF-kappa B is a downstream target of AKT and that chemothera-

peutics induce AKT activation, IκBα phosphorylation and degradation, and finally, NF-kappa B activation. Inducible AKT and NF-kappa B activities are involved in the chemoresistance of gastric cancer cells. The activation of NF-kappa B is one part of the mechanism of chemoresistance induced by AKT[77]. Survivin is another downstream target of AKT. In cisplatin-resistant gastric cancer cells, higher levels of survivin and p-AKT have been observed. According to one study, specific inhibition of AKT reduced the expression of survivin and enhanced the sensitivity of cisplatin-resistant cells to cisplatin[78]. Another study showed that the up-regulation of p-AKT expression could confer multidrug resistance in gastric cancer cells through the up-regulation of BCL-2 expression and the down-regulation of BAX expression[79].

Because the PI3K/AKT pathway plays a vital role in chemoresistance in gastric cancer, the targeting of PI3K/AKT has emerged as a promising approach to reverse chemotherapy resistance. A recent study reported that LY294002, a selective inhibitor of PI3K, might overcome intrinsic and acquired resistance to 5-FU *via* the down-regulation of activated p-AKT and mitochondria-dependent apoptosis in gastric cancer cells[80]. An AKT inhibitor (MK-2206) has also been demonstrated to augment the efficacy of chemotherapeutics in gastric cancer, but the magnitude of synergy depends on the treatment sequence. Furthermore, in one study, MK-2206 administered before chemotherapy resulted in the highest synergistic effect compared to the effects when it was administered after or concurrently with chemotherapy[81].

Mitogen-activated protein kinase pathway

The mitogen-activated protein kinase (MAPK) signaling pathway is widely expressed in multicellular organisms, where it plays a critical role in multiple biological processes, such as cell proliferation, differentiation, and cell death. Dysregulation of the MAPK signaling pathway is associated with the occurrence and progression of various cancers including gastric carcinoma[82]. Moreover, numerous studies have demonstrated that the MAPK pathway is also involved in chemotherapy resistance in gastric cancer. According to one study, phosphorylated mitogen-activated protein kinase (p-MAPK) was positive in 59.6% of patients with metastatic gastric cancer. Moreover, the expression of p-MAPK in primary tumors and metastatic lesions was similar. The overall survival was found to be significantly shorter in p-MAPK-positive patients. This indicated that p-MAPK expression might be a potential negative prognostic parameter in patients with metastatic gastric cancer who are treated with chemotherapy[83]. The activation of the p38-MAPK pathway was found in vincristine-resistant gastric cancer SGC7901/VCR cells and was determined to be responsible for the modulation of multidrug resistance[84]. In addition, the inhibition of p38 MAPK significantly increased gastric cancer cell sensitivity to doxorubicin through the induced expression of the pro-apoptotic protein BAX and a concomitant decrease in BCL-2 expression[85].

TUMOR MICROENVIRONMENT

The tumor microenvironment consists of the extracellular matrix (ECM), various cells including cancer-associated fibroblasts, immune and inflammatory cells, and blood or lymph vessels. Increasing evidence has shown that the tumor microenvironment has multiple functions in tumorigenesis, invasion, and metastasis, as well as in drug resistance.

Hypoxia

Hypoxia, which is a common feature of solid tumors, results in tumor progression and treatment resistance. HIF-1α is one of the most important regulators of the cellular response to hypoxia. HIF-1α expression was found to be positive in 65.6% of gastric cancers. The overexpression of HIF-1α was found to be an indicator of poor prognosis for patients with gastric cancer and was significantly correlated with histology, depth of invasion, VEGF expression, and MVD[86]. It has also been reported that HIF-1α expression could predict the response of patients with advanced gastric cancer to 5-FU-based adjuvant chemotherapy[87]. Another study showed that HIF-1α determines gastric cancer chemosensitivity through the modulation of p53 and NF-kappa B[88]. Additional studies demonstrated that HIF-1α overexpression increases the expression of BCL-2, decreases the expression of BAX, and also significantly induces the expression of ABCB1 and ABCC1. This indicates that HIF-1α may confer hypoxia-induced drug resistance *via* the inhibition of drug-induced apoptosis and decreases in intracellular drug accumulation[89].

Alterations of the extracellular matrix

The ECM is a complicated network of multifunctional molecules that influence major malignant phenotypes of cancer cells, including oncogenesis, progression and drug resistance. Laminin and collagen Ⅳ are natural basement membrane components that constitute a specific ECM that maintains malignant phenotypes in gastric adenocarcinoma cells[90]. Recent findings showed that the adhesive ability of multidrug-resistant gastric cancer cells was significantly increased compared with parental cells, which were sensitive to chemotherapeutic drugs. The ECM component laminin increased the resistance of gastric cancer cells to vincristine and adriamycin by binding to the receptor MGr1-Ag/37LRP. This suggested that the chemoresistant phenotype of gastric cancer cells is associated with a state of increased cell adhesion. Laminin can modify the response to chemotherapeutic agents by various mechanisms, including regulation of MDR-related proteins (ABCB1 and ABCC1), apoptosis-related genes (*BCL-2* and *BAX*), and signaling pathways (PI3K/AKT and MAPK/ERK)[91,92]. It has been demonstrated that extracellular high mobility group box chromosomal protein 1 might promote drug resistance to adriamycin and vincristine *via* the up-regulation of ABCB1 in human gastric adenocarcinoma cells[93].

Cytokines and growth factors

Soluble factors in the tumor microenvironment such as cytokines and growth factors exhibit key functions in chemotherapeutic resistance, as they maintain the activation of various survival-related signaling pathways. In a recent study, the serum levels of 52 types of cytokines and angiogenic factors were measured in 68 patients with gastric cancer who were treated with fluoropyrimidine and platinum combination chemotherapy. The following eleven cytokines and angiogenic factors were found to be independently correlated with poor overall survival: Interleukin-2 receptor-alpha, growth-regulated alpha protein, hepatocyte growth factor, macrophage colony-stimulating factor, stromal cell-derived factor, IL-6, IL-8, IL-10, interferon-gamma, vascular endothelial growth factor, and osteopontin[94]. IL-33 has been reported to confer resistance to chemotherapy in gastric cancer cells through activation of the JNK signaling pathway[95]. IL-6 can trigger the activation of STAT3 and has been found to be associated with acquisition of resistance of gastric cancer cells to trastuzumab[96]. Tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) is a member of the TNF superfamily of structurally related cytokines. It was revealed that TWEAK promotes resistance to 5-FU in gastric cancer cells through NF-kappa B activation[97].

CONCLUSION

Resistance to chemotherapy is a major challenge for patients who currently undergo therapy for gastric cancer. A wide range of molecular mechanisms of chemoresistance has been implicated in gastric cancer, including reduced intracellular concentrations of drugs and alterations of drug targets. The dysregulation of cell survival and death signaling pathways can also lead to resistance to chemotherapeutic drugs. In addition, the interactions between cancer cells and the tumor microenvironment also plays an important role in chemoresistance in gastric cancer. These emerging findings are very helpful for the development of personalized therapies based on the prediction of the chemosensitivity of cancer cells as well as for the establishment of novel therapeutic strategies to reverse the chemoresistance of tumors. However, the mechanisms of chemoresistance are complex and multifactorial. The chemotherapeutic resistance of tumors may be caused by different molecular mechanisms in different patients due to tumor heterogeneity and drug variety. Therefore, more extensive studies are needed for a more comprehensive elucidation of the mechanisms of chemotherapy resistance in gastric cancer.

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P- Reviewer: Nishiyama M, Paydas S **S- Editor**: Qi Y
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