**Name of journal: *World Journal of Gastrointestinal Oncology***

**ESPS Manuscript NO: 26016**

**Manuscript Type: Review**

**Molecular mechanisms of chemoresistance in gastric cancer**

Shi WJ *et al.* Mechanisms of chemoresistance in gastric cancer

**Wen-Jia Shi, Jin-Bo Gao**

**Wen-Jia Shi,** Department of Pediatric Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei Province, China

**Jin-Bo Gao,** Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei Province, China

**Author contributions:** Shi WJ and Gao JB 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.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Correspondence to: Jin-Bo Gao, Associate Professor,** Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan 430022, Hubei Province, China.gaojinbo@163.com

**Telephone:** +86-27-85351619

**Fax:** +86-27-85351619

**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:**

**Published online:**

**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:** Gastric cancer; Chemotherapy; Drug resistance

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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; In press

**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 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 (MRP), 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 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 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 HIF-1a), 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-fluorouracil 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-fluorouracil 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-fluorouracil 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 2rendered 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-fluorouracil 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 phosphatidylinositol-3 kinase (PI3K) activity, have been reported in gastric cancer[65,66]. The expression of AKT and phosphorylated AKT (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-fluorouracil, 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 chemotherapeutics 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 phosphorylated 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].

***MAPK 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. Hypoxia-inducible factor-1alpha (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-fluorouracil-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 extracellular matrix (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 (IL-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-like weak inducer of apoptosis (TWEAK) is a member of the tumor necrosis factor (TNF) superfamily of structurally related cytokines. It was revealed that TWEAK promotes resistance to 5-fluorouracil 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.

**REFERENCES**

1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

2 **Wöhrer SS**, Raderer M, Hejna M. Palliative chemotherapy for advanced gastric cancer. *Ann Oncol* 2004; **15**: 1585-1595 [PMID: 15520058 DOI: 10.1093/annonc/mdh422]

3 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992 DOI: 10.1056/NEJMoa055531]

4 **Casaretto L**, Sousa PL, Mari JJ. Chemotherapy versus support cancer treatment in advanced gastric cancer: a meta-analysis. *Braz J Med Biol Res* 2006; **39**: 431-440 [PMID: 16612465 DOI: 10.1590/S0100-879X2006000400002]

5 **Wagner AD**, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006; **24**: 2903-2909 [PMID: 16782930 DOI: 10.1200/JCO.2005.05.0245]

6 **Morin PJ**. Drug resistance and the microenvironment: nature and nurture. *Drug Resist Updat* 2003; **6**: 169-172 [PMID: 12962682 DOI: 10.1016/S1368-7646(03)00059-1]

7 **Sugimoto Y**, Asami N, Tsuruo T. Expression of P-glycoprotein mRNA in human gastric tumors. *Jpn J Cancer Res* 1989; **80**: 993-999 [PMID: 2575610 DOI: 10.1111/j.1349-7006.1989.tb01639.x]

8 **Wallner J**, Depisch D, Gsur A, Götzl M, Haider K, Pirker R. MDR1 gene expression and its clinical relevance in primary gastric carcinomas. *Cancer* 1993; **71**: 667-671 [PMID: 8431845 DOI: 10.1002/1097-0142(19930201)71]

9 **Gürel S**, Yerci O, Filiz G, Dolar E, Yilmazlar T, Nak SG, Gülten M, Zorluoğlu A, Memik F. High expression of multidrug resistance-1 (MDR-1) and its relationship with multiple prognostic factors in gastric carcinomas in patients in Turkey. *J Int Med Res* 1999; **27**: 79-84 [PMID: 10446694]

10 **Choi JH**, Lim HY, Joo HJ, Kim HS, Yi JW, Kim HC, Cho YK, Kim MW, Lee KB. Expression of multidrug resistance-associated protein1,P-glycoprotein, and thymidylate synthase in gastric cancer patients treated with 5-fluorouracil and doxorubicin-based adjuvant chemotherapy after curative resection. *Br J Cancer* 2002; **86**: 1578-1585 [PMID: 12085207 DOI: 10.1038/sj.bjc.6600305]

11 **de Oliveira J**, Felipe AV, Neto RA, Oshima CT, de Souza Silva M, Forones NM. Association between ABCB1 immunohistochemical expression and overall survival in gastric cancer patients. *Asian Pac J Cancer Prev* 2014; **15**: 6935-6938 [PMID: 25169549 DOI: 10.7314/APJCP.2014.15.16.6935]

12 **Park JG**, Kramer BS, Lai SL, Goldstein LJ, Gazdar AF. Chemosensitivity patterns and expression of human multidrug resistance-associated MDR1 gene by human gastric and colorectal carcinoma cell lines. *J Natl Cancer Inst* 1990; **82**: 193-198 [PMID: 1967320 DOI: 10.1093/jnci/82.3.193]

13 **Robey-Cafferty SS**, Rutledge ML, Bruner JM. Expression of a multidrug resistance gene in esophageal adenocarcinoma. Correlation with response to chemotherapy and comparison with gastric adenocarcinoma. *Am J Clin Pathol* 1990; **93**: 1-7 [PMID: 1967201 DOI: 10.1093/ajcp/93.1.1]

14 **Orita H**, Maehara Y, Anai H, Baba H, Kusumoto H, Korenaga D, Sugimachi K. Expression of P-glycoprotein influences resistance against anthracyclines in clinical gastric carcinomas. *Semin Surg Oncol* 1994; **10**: 135-139 [PMID: 7914378 DOI: 10.1002/ssu.2980100215]

15 **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**: 34-42 [PMID: 20233511 DOI: 10.1177/147323001003800104]

16 **Chung HC**, Gong SJ, Yoo NC, Noh SH, Kim JH, Roh JK, Min JS, Kim BS, Lee KB. P-glycoprotein as an intermediate end point of drug resistance to neoadjuvant chemotherapy in locally advanced gastric cancer. *Yonsei Med J* 1996; **37**: 397-404 [PMID: 9048492 DOI: 10.3349/ymj.1996.37.6.397]

17 **Monden N**, Abe S, Hishikawa Y, Yoshimura H, Kinugasa S, Dhar DK, Tachibana M, Nagasue N. The role of P-glycoprotein in human gastric cancer xenografts in response to chemotherapy. *Int J Surg Investig* 1999; **1**: 3-10 [PMID: 11817335]

18 **Stege A**, Priebsch A, Nieth C, Lage H. Stable and complete overcoming of MDR1/P-glycoprotein-mediated multidrug resistance in human gastric carcinoma cells by RNA interference. *Cancer Gene Ther* 2004; **11**: 699-706 [PMID: 15375376 DOI: 10.1038/sj.cgt.7700751]

19 **Hu WQ**, Peng CW, Li Y. The expression and significance of P-glycoprotein, lung resistance protein and multidrug resistance-associated protein in gastric cancer. *J Exp Clin Cancer Res* 2009; **28**:144 [PMID: 19930704 DOI: 10.1186/1756-9966-28-144]

20 **Yu P**, Du Y, Cheng X, Yu Q, Huang L, Dong R. Expression of multidrug resistance-associated proteins and their relation to postoperative individualized chemotherapy in gastric cancer. *World J Surg Oncol* 2014; **12**: 307 [PMID: 25304659 DOI: 10.1186/1477-7819-12-307]

21 **Bentires-Alj M**, Barbu V, Fillet M, Chariot A, Relic B, Jacobs N, Gielen J, Merville MP, Bours V. NF-kappaB transcription factor induces drug resistance through MDR1 expression in cancer cells. *Oncogene* 2003; **22**: 90-97 [PMID: 12527911 DOI: 10.1038/sj.onc.1206056]

22 **Gu KS**, Chen Y. Mechanism of P-glycoprotein expression in the SGC7901 human gastric adenocarcinoma cell line induced by cyclooxygenase-2. *Asian Pac J Cancer Prev* 2012; **13**: 2379-2383 [PMID: 22901225 DOI: 10.7314/APJCP.2012.13.5.2379]

23 **Zhang Y**, Qu X, Hu X, Yang X, Hou K, Teng Y, Zhang J, Sada K, Liu Y. Reversal of P-glycoprotein-mediated multi-drug resistance by the E3 ubiquitin ligase Cbl-b in human gastric adenocarcinoma cells. *J Pathol* 2009; **218**: 248-255 [PMID: 19274672 DOI: 10.1002/path.2533]

24 **Shang Y,** Zhang Z, Liu Z, Feng B, Ren G, Li K, Zhou L, Sun Y, Li M, Zhou J, An Y, Wu K, Nie Y, Fan D. miR-508-5p regulates multidrug resistance of gastric cancer by targeting ABCB1 and ZNRD1. *Oncogene* 2014; **33**: 3267–3276 [PMID: 23893241 DOI: 10.1038/onc.2013.297 DOI: 10.1038/onc.2013.297]

25 **Zhang Y**, Lu Q, Cai X. MicroRNA-106a induces multidrug resistance in gastric  cancer by targeting RUNX3. *FEBS Lett* 2013; **587**: 3069–3075 [PMID: 23932924 DOI: 10.1016/j.febslet.2013.06.058]

26 **Zhao X**, Yang L, Hu J. Down-regulation of miR-27a might inhibit  proliferation and drug resistance of gastric cancer cells. *J Exp Clin Cancer Res* 2011; **30**: 55 [PMID: 21569481 DOI: 10.1186/1756-9966-30-55]

27 **Zhang XW**, Bu P, Liu L, Zhang XZ, Li J. Overexpression of long non-coding RNA PVT1 in gastric cancer cells promotes the development of multidrug resistance. *Biochem Biophys Res Commun* 2015; **462**: 227-232 [PMID: 25956062 DOI: 10.1016/j.bbrc.2015.04.121]

28 **Peters WH**, Wormskamp NG, Thies E. Expression of glutathione S-transferases in normal gastric mucosa and in gastric tumors. *Carcinogenesis* 1990; **11**: 1593-1596 [PMID: 2401049 DOI: 10.1093/carcin/11.9.1593]

29 **Schipper DL**, Wagenmans MJ, Peters WH, Wils JA, Wagener DJ. Glutathione S-transferases and iododeoxyuridine labelling index during chemotherapy of gastric cancer. *Anticancer Res* 2000; **20**: 1705-1710 [PMID: 10928096]

30 **Okuyama T**, Maehara Y, Endo K, Baba H, Adachi Y, Kuwano M, Sugimachi K. Expression of glutathione S-transferase-pi and sensitivity of human gastric cancer cells to cisplatin. *Cancer* 1994; **74**: 1230-1236 [PMID: 8055443 DOI: 10.1002/1097-0142(19940815)74]

31 **Kodera Y**, Isobe K, Yamauchi M, Kondo K, Akiyama S, Ito K, Nakashima I, Takagi H. Expression of glutathione-S-transferases alpha and pi in gastric cancer: a correlation with cisplatin resistance. *Cancer Chemother Pharmacol* 1994; **34**: 203-208 [PMID: 8004752 DOI: 10.1007/BF00685078]

32 **Rocha Gda G**, Oliveira RR, Kaplan MA, Gattass CR. 3β-Acetyl tormentic acid reverts MRP1/ABCC1 mediated cancer resistance through modulation of intracellular levels of GSH and inhibition of GST activity. *Eur J Pharmacol* 2014; **741**: 140-149 [PMID: 25111243 DOI: 10.1016/j.ejphar.2014.07.054]

33 **Kodera Y**, Ito S, Fujiwara M, Mochizuki Y, Nakayama G, Ohashi N, Koike M, Yamamura Y, Nakao A. Gene expression of 5-fluorouracil metabolic enzymes in primary gastric cancer: correlation with drug sensitivity against 5-fluorouracil. *Cancer Lett* 2007; **252**: 307-313 [PMID: 17303323 DOI: 10.1016/j.canlet.2007.01.006]

34 **Gao J**, Lu M, Yu JW, Li YY, Shen L. Thymidine Phosphorylase/β-tubulin III expressions predict the response in Chinese advanced gastric cancer patients receiving first-line capecitabine plus paclitaxel. *BMC Cancer* 2011; **11**: 177 [PMID: 21586171 DOI: 10.1186/1471-2407-11-177]

35 **Hua D**, Huang ZH, Mao Y, Deng JZ. Thymidylate synthase and thymidine phosphorylase gene expression as predictive parameters for the efficacy of 5-fluorouracil-based adjuvant chemotherapy for gastric cancer. *World J Gastroenterol* 2007; **13**: 5030-5034 [PMID: 17854149 DOI: 10.3748/wjg.v13.i37.5030]

36 **Yabuki N**, Sasano H, Kato K, Ohara S, Toyota T, Nagura H, Miyaike M, Nozaki N, Kikuchi A. Immunohistochemical study of DNA topoisomerase II in human gastric disorders. *Am J Pathol* 1996; **149**: 997-1007 [PMID: 8780403]

37 **Kim R**, Ohi Y, Inoue H, Toge T. Expression and relationship between topoisomerase I and II alpha genes in tumor and normal tissues in esophageal, gastric and colon cancers. *Anticancer Res* 1999; **19**: 5393-5398 [PMID: 10697567]

38 **Liu HQ**, Zhang SL, Song S. HER-2/neu and TOPIIa expression in gastric cancer reflect disease severity. *Hepatogastroenterology* 2012; **59**: 1290-1293 [PMID: 22281973 DOI: 10.5754/hge11844]

39 **Wang G**, Huang H, Gao J, Chen P, You W, Wu B, Wang M. Tissue microarray analysis of topoisomerase IIalpha protein in gastric adenocarcinomas: histogenetic and prognostic implications. *Cancer Genomics Proteomics* 2011; **8**: 127-133 [PMID: 21518818]

40 **Son YS**, Suh JM, Ahn SH, Kim JC, Yi JY, Hur KC, Hong WS, Muller MT, Chung IK. Reduced activity of topoisomerase II in an Adriamycin-resistant human stomach-adenocarcinoma cell line. *Cancer Chemother Pharmacol* 1998; **41**: 353-360 [PMID: 9523730 DOI: 10.1007/s002800050751]

41 **Geng M**, Wang L, Chen X, Cao R, Li P. The association between chemosensitivity and Pgp, GST-π and Topo II expression in gastric cancer. *Diagn Pathol* 2013; **8**: 198 [PMID: 24326092 DOI: 10.1186/1746-1596-8-198]

42 **Mimori K**, Sadanaga N, Yoshikawa Y, Ishikawa K, Hashimoto M, Tanaka F, Sasaki A, Inoue H, Sugimachi K, Mori M. Reduced tau expression in gastric cancer can identify candidates for successful Paclitaxel treatment. *Br J Cancer* 2006; **94**: 1894-1897 [PMID: 16721363]

43 **He W**, Zhang D, Jiang J, Liu P, Wu C. The relationships between the chemosensitivity of human gastric cancer to paclitaxel and the expressions of class III β-tubulin, MAPT, and survivin. *Med Oncol* 2014; **31**: 950 [PMID: 24722794 DOI: 10.1007/s12032-014-0950-3]

44 **Wu H**, Huang M, Lu M, Zhu W, Shu Y, Cao P, Liu P. Regulation of microtubule-associated protein tau (MAPT) by miR-34c-5p determines the chemosensitivity of gastric cancer to paclitaxel. *Cancer Chemother Pharmacol* 2013; **71**: 1159-1171 [PMID: 23423488 DOI: 10.1007/s00280-013-2108-y]

45 **Kang MH**, Reynolds CP. Bcl-2 inhibitors: targeting mitochondrial apoptotic pathways in cancer therapy. *Clin Cancer Res* 2009; **15**: 1126-1132 [PMID: 19228717 DOI: 10.1158/1078-0432.CCR-08-0144]

46 **Bhola PD**, Letai A. Mitochondria-Judges and Executioners of Cell Death Sentences. *Mol Cell* 2016; **61**: 695-704 [PMID: 26942674 DOI: 10.1016/j.molcel.2016.02.019]

47 **Geng M**, Wang L, Li P. Correlation between chemosensitivity to anticancer drugs and Bcl-2 expression in gastric cancer. *Int J Clin Exp Pathol* 2013; **6**: 2554-2559 [PMID: 24228120]

48 **Li Y**, Tan BB, Zhao Q, Fan LQ, Liu Y, Hao YJ, Zhao XF. Tumor chemosensitivity is correlated with expression of multidrug resistance associated factors in variously differentiated gastric carcinoma tissues. *Hepatogastroenterology* 2013; **60**: 213-216 [PMID: 22945336]

49 **Yu DF**, Wu FR, Liu Y, Liu H, Xia Q. Bcl-2 gene silence enhances the sensitivity toward 5-Fluorouracil in gastric adenocarcinoma cells. *Biomed Pharmacother* 2013; **67**: 615-619 [PMID: 23684481 DOI: 10.1016/j.biopha.2013.03.007]

50 **Cho HJ**, Baek KE, Park SM, Kim IK, Nam IK, Choi YL, Park SH, Im MJ, Choi J, Ryu J, Kim JW, Lee CW, Kang SS, Yoo J. RhoGDI2 confers gastric cancer cells resistance against cisplatin-induced apoptosis by upregulation of Bcl-2 expression. *Cancer Lett* 2011; **311**: 48-56 [PMID: 21752536 DOI: 10.1016/j.canlet.2011.06.024]

51 **Sacconi A**, Biagioni F, Canu V, Mori F, Di Benedetto A, Lorenzon L, Ercolani C, Di Agostino S, Cambria AM, Germoni S, Grasso G, Blandino R, Panebianco V, Ziparo V, Federici O, Muti P, Strano S, Carboni F, Mottolese M, Diodoro M, Pescarmona E, Garofalo A, Blandino G. miR-204 targets Bcl-2 expression and enhances responsiveness of gastric cancer. *Cell Death Dis* 2012; **3**: e423 [PMID: 23152059 DOI: 10.1038/cddis.2012.160]

52 **Zhu W**, Shan X, Wang T, Shu Y, Liu P. miR-181b modulates multidrug resistance by targeting BCL2 in human cancer cell lines. *Int J Cancer* 2010; **127**: 2520-2529 [PMID: 20162574 DOI: 10.1002/ijc.25260]

53 **Xia L**, Zhang D, Du R, Pan Y, Zhao L, Sun S, Hong L, Liu J, Fan D. miR-15b and miR-16 modulate multidrug resistance by targeting BCL2 in human gastric cancer cells. *Int J Cancer* 2008; **123**: 372-379 [PMID: 18449891 DOI: 10.1002/ijc.23501]

54 **Jeong SH**, Han JH, Kim JH, Ahn MS, Hwang YH, Lee HW, Kang SY, Park JS, Choi JH, Lee KJ, Sheen SS, Lim HY. Bax predicts outcome in gastric cancer patients treated with 5-fluorouracil, leucovorin, and oxaliplatin palliative chemotherapy. *Dig Dis Sci* 2011; **56**: 131-138 [PMID: 20503071 DOI: 10.1007/s10620-010-1280-8]

55 **Sawa H**, Kobayashi T, Mukai K, Zhang W, Shiku H. Bax overexpression enhances cytochrome c release from mitochondria and sensitizes KATOIII gastric cancer cells to chemotherapeutic agent-induced apoptosis. *Int J Oncol* 2000; **16**: 745-749 [PMID: 10717243]

56 **Gao J**, Tian Y, Zhang J. Overexpression of interferon regulatory factor 1 enhances chemosensitivity to 5-fluorouracil in gastric cancer cells. *J Cancer Res Ther* 2012; **8**: 57-61 [PMID: 22531515 DOI: 10.4103/0973-1482.95175]

57 **Gao J**, Senthil M, Ren B, Yan J, Xing Q, Yu J, Zhang L, Yim JH. IRF-1 transcriptionally upregulates PUMA, which mediates the mitochondrial apoptotic pathway in IRF-1-induced apoptosis in cancer cells. *Cell Death Differ* 2010; **17**: 699-709 [PMID: 19851330 DOI: 10.1038/cdd.2009.156]

58 **Tahara M**, Ochiai A, Fujimoto J, Boku N, Yasui W, Ohtsu A, Tahara E, Yoshida S. Expression of thymidylate synthase, thymidine phosphorylase, dihydropyrimidine dehydrogenase, E2F-1, Bak, Bcl-X, and Bcl-2, and clinical outcomes for gastric cancer patients treated with bolus 5-fluorouracil. *Oncol Rep* 2004; **11**: 9-15 [PMID: 14654896]

59 **Tsujitani S**, Saito H, Wakatsuki T, Ikeguchi M, Shirabe K, Morita M, Kakeji Y, Yano T, Maehara Y. Relationship between expression of apoptosis-related proteins and the efficacy of postoperative chemotherapy in patients with T3 gastric cancer. *Surg Today* 2012; **42**: 225-232 [PMID: 22143356 DOI: 10.1007/s00595-011-0062-z]

60 **Fenoglio-Preiser CM**, Wang J, Stemmermann GN, Noffsinger A. TP53 and gastric carcinoma: a review. *Hum Mutat* 2003; **21**: 258-270 [PMID: 12619111]

61 **Bellini MF**, Cadamuro AC, Succi M, Proença MA, Silva AE. Alterations of the TP53 gene in gastric and esophageal carcinogenesis. *J Biomed Biotechnol* 2012; **2012**: 891961 [PMID: 22919278 DOI: 10.1155/2012/891961]

62 **Xu HY**, Xu WL, Wang LQ, Chen MB, Shen HL. Relationship between p53 status and response to chemotherapy in patients with gastric cancer: a meta-analysis. *PLoS One* 2014; **9**: e95371 [PMID: 24740294 DOI: 10.1371/journal.pone.0095371]

63 **Chen GX**, Zheng LH, Liu SY, He XH. rAd-p53 enhances the sensitivity of human gastric cancer cells to chemotherapy. *World J Gastroenterol* 2011; **17**: 4289-4297 [PMID: 22090785 DOI: 10.3748/wjg.v17.i38.4289]

64 **Kim CW**, Lu JN, Go SI, Jung JH, Yi SM, Jeong JH, Hah YS, Han MS, Park JW, Lee WS, Min YJ. p53 restoration can overcome cisplatin resistance through inhibition of Akt as well as induction of Bax. *Int J Oncol* 2013; **43**: 1495-1502 [PMID: 23970333 DOI: 10.3892/ijo.2013.2070]

65 **Li VS**, Wong CW, Chan TL, Chan AS, Zhao W, Chu KM, So S, Chen X, Yuen ST, Leung SY. Mutations of PIK3CA in gastric adenocarcinoma. *BMC Cancer* 2005; **5**: 29 [PMID: 15784156]

66 **Velho S**, Oliveira C, Ferreira A, Ferreira AC, Suriano G, Schwartz S, Duval A, Carneiro F, Machado JC, Hamelin R, Seruca R. The prevalence of PIK3CA mutations in gastric and colon cancer. *Eur J Cancer* 2005; **41**: 1649-1654 [PMID: 15994075]

67 **Nam SY**, Lee HS, Jung GA, Choi J, Cho SJ, Kim MK, Kim WH, Lee BL. Akt/PKB activation in gastric carcinomas correlates with clinicopathologic variables and prognosis. *APMIS* 2003; **111**: 1105-1113 [PMID: 14678019]

68 **Cinti C**, Vindigni C, Zamparelli A, La Sala D, Epistolato MC, Marrelli D, Cevenini G, Tosi P. Activated Akt as an indicator of prognosis in gastric cancer. *Virchows Arch* 2008; **453**: 449-455 [PMID: 18841391 DOI: 10.1007/s00428-008-0676-8]

69 **Oki E**, Baba H, Tokunaga E, Nakamura T, Ueda N, Futatsugi M, Mashino K, Yamamoto M, Ikebe M, Kakeji Y, Maehara Y. Akt phosphorylation associates with LOH of PTEN and leads to chemoresistance for gastric cancer. *Int J Cancer* 2005; **117**: 376-380 [PMID: 15900596]

70 **Murakami D**, Tsujitani S, Osaki T, Saito H, Katano K, Tatebe S, Ikeguchi M. Expression of phosphorylated Akt (pAkt) in gastric carcinoma predicts prognosis and efficacy of chemotherapy. *Gastric Cancer* 2007; **10**: 45-51 [PMID: 17334718]

71 **Liu SQ**, Yu JP, Yu HG, Lv P, Chen HL. Activation of Akt and ERK signalling pathways induced by etoposide confer chemoresistance in gastric cancer cells. *Dig Liver Dis* 2006; **38**: 310-318 [PMID: 16527552]

72 **Yu HG**, Ai YW, Yu LL, Zhou XD, Liu J, Li JH, Xu XM, Liu S, Chen J, Liu F, Qi YL, Deng Q, Cao J, Liu SQ, Luo HS, Yu JP. Phosphoinositide 3-kinase/Akt pathway plays an important role in chemoresistance of gastric cancer cells against etoposide and doxorubicin induced cell death. *Int J Cancer* 2008; **122**: 433-443 [PMID: 17935137]

73 **Zhang LL**, Zhang J, Shen L, Xu XM, Yu HG. Overexpression of AKT decreases the chemosensitivity of gastric cancer cells to cisplatin in vitro and in vivo. *Mol Med Rep* 2013; **7**: 1387-1390 [PMID: 23546174 DOI: 10.3892/mmr.2013.1400]

74 **Han Z**, Hong L, Wu K, Han S, Shen H, Liu C, Han Y, Liu Z, Han Y, Fan D. Reversal of multidrug resistance of gastric cancer cells by downregulation of Akt1 with Akt1 siRNA. *J Exp Clin Cancer Res* 2006; **25**: 601-606 [PMID: 17310852]

75 **Bellacosa A**, Kumar CC, Di Cristofano A, Testa JR. Activation of AKT kinases in cancer: implications for therapeutic targeting. *Adv Cancer Res* 2005; **94**: 29-86 [PMID: 16095999]

76 **Sukawa Y**, Yamamoto H, Nosho K, Kunimoto H, Suzuki H, Adachi Y, Nakazawa M, Nobuoka T, Kawayama M, Mikami M, Matsuno T, Hasegawa T, Hirata K, Imai K, Shinomura Y. Alterations in the human epidermal growth factor receptor 2-phosphatidylinositol 3-kinase-v-Akt pathway in gastric cancer. *World J Gastroenterol* 2012; **18**: 6577-6586 [PMID: 23236232 DOI: 10.3748/wjg.v18.i45.6577]

77 **Yu LL**, Dai N, Yu HG, Sun LM, Si JM. Akt associates with nuclear factor kappaB and plays an important role in chemoresistance of gastric cancer cells. *Oncol Rep* 2010; **24**: 113-119 [PMID: 20514451]

78 **Sun XP**, Dong X, Lin L, Jiang X, Wei Z, Zhai B, Sun B, Zhang Q, Wang X, Jiang H, Krissansen GW, Qiao H, Sun X. Up-regulation of survivin by AKT and hypoxia-inducible factor 1α contributes to cisplatin resistance in gastric cancer. *FEBS J* 2014; **281**: 115-128 [PMID: 24165223 DOI: 10.1111/febs.12577]

79 **Han Z**, Hong L, Han Y, Wu K, Han S, Shen H, Li C, Yao L, Qiao T, Fan D. Phospho Akt mediates multidrug resistance of gastric cancer cells through regulation of P-gp, Bcl-2 and Bax. *J Exp Clin Cancer Res* 2007; **26**: 261-268 [PMID: 17725107]

80 **Shin JY**, Kim JO, Lee SK, Chae HS, Kang JH. LY294002 may overcome 5-FU resistance via down-regulation of activated p-AKT in Epstein-Barr virus-positive gastric cancer cells. *BMC Cancer* 2010; **10**: 425 [PMID: 20704765 DOI: 10.1186/1471-2407-10-425]

81 **Almhanna K**, Cubitt CL, Zhang S, Kazim S, Husain K, Sullivan D, Sebti S, Malafa M. MK-2206, an Akt inhibitor, enhances carboplatinum/paclitaxel efficacy in gastric cancer cell lines. *Cancer Biol Ther* 2013; **14**: 932-936 [PMID: 23917345 DOI: 10.4161/cbt.25939]

82 **Yang M**, Huang CZ. Mitogen-activated protein kinase signaling pathway and invasion and metastasis of gastric cancer. *World J Gastroenterol* 2015; **21**: 11673-11679 [PMID: 26556994 DOI: 10.3748/wjg.v21.i41.11673]

83 **Atmaca A**, Pauligk C, Steinmetz K, Altmannsberger HM, Jäger E, Al-Batran SE. Prognostic impact of phosphorylated mitogen-activated protein kinase expression in patients with metastatic gastric cancer. *Oncology* 2011; **80**: 130-134 [PMID: 21677458 DOI: 10.1159/000329063]

84 **Guo X**, Ma N, Wang J, Song J, Bu X, Cheng Y, Sun K, Xiong H, Jiang G, Zhang B, Wu M, Wei L. Increased p38-MAPK is responsible for chemotherapy resistance in human gastric cancer cells. *BMC Cancer* 2008; **8**: 375 [PMID: 19091131 DOI: 10.1186/1471-2407-8-375]

85 **Tan W**, Yu HG, Luo HS. Inhibition of the p38 MAPK pathway sensitizes human gastric cells to doxorubicin treatment in vitro and in vivo. *Mol Med Rep* 2014; **10**: 3275-3281 [PMID: 25270341 DOI: 10.3892/mmr.2014.2598]

86 **Isobe T**, Aoyagi K, Koufuji K, Shirouzu K, Kawahara A, Taira T, Kage M. Clinicopathological significance of hypoxia-inducible factor-1 alpha (HIF-1α) expression in gastric cancer. *Int J Clin Oncol* 2013; **18**: 293-304 [PMID: 22350022 DOI: 10.1007/s10147-012-0378-8]

87 **Nakamura J**, Kitajima Y, Kai K, Mitsuno M, Ide T, Hashiguchi K, Hiraki M, Miyazaki K. Hypoxia-inducible factor-1alpha expression predicts the response to 5-fluorouracil-based adjuvant chemotherapy in advanced gastric cancer. *Oncol Rep* 2009; **22**: 693-699 [PMID: 19724845]

88 **Rohwer N**, Dame C, Haugstetter A, Wiedenmann B, Detjen K, Schmitt CA, Cramer T. Hypoxia-inducible factor 1alpha determines gastric cancer chemosensitivity via modulation of p53 and NF-kappaB. *PLoS One* 2010; **5**: e12038 [PMID: 20706634 DOI: 10.1371/journal.pone.0012038]

89 **Liu L**, Ning X, Sun L, Zhang H, Shi Y, Guo C, Han S, Liu J, Sun S, Han Z, Wu K, Fan D. Hypoxia-inducible factor-1 alpha contributes to hypoxia-induced chemoresistance in gastric cancer. *Cancer Sci* 2008; **99**: 121-128 [PMID: 17953712]

90 **Nakamura K**, Mori M, Enjoji M. Distribution of basement membrane antigens in clinical gastric adenocarcinomas: an immunohistochemical study. *J Clin Pathol* 1987; **40**: 1418-1423 [PMID: 3323249]

91 **Sun L**, Liu L, Liu X, Wang Y, Li M, Yao L, Yang J, Ji G, Guo C, Pan Y, Liang S, Wang B, Ding J, Zhang H, Shi Y. Gastric cancer cell adhesion to laminin enhances acquired chemotherapeutic drug resistance mediated by MGr1-Ag/37LRP. *Oncol Rep* 2014; **32**: 105-114 [PMID: 24840404 DOI: 10.3892/or.2014.3184]

92 **Sun L**, Liu L, Liu X, Wang Y, Li M, Yao L, Yang J, Ji G, Guo C, Pan Y, Liang S, Wang B, Ding J, Zhang H, Shi Y. MGr1-Ag/37LRP induces cell adhesion-mediated drug resistance through FAK/PI3K and MAPK pathway in gastric cancer. *Cancer Sci* 2014; **105**: 651-659 [PMID: 24703465 DOI: 10.1111/cas.12414]

93 **Yin Y**, Li W, Deng M, Zhang P, Shen Q, Wang G, Tao K. Extracellular high mobility group box chromosomal protein 1 promotes drug resistance by increasing the expression of P‑glycoprotein expression in gastric adenocarcinoma cells. *Mol Med Rep* 2014; **9**: 1439-1443 [PMID: 24549588 DOI: 10.3892/mmr.2014.1961]

94 **Yin Y,** Li W, Deng M, Zhang P, Shen Q, Wang G, Tao K.Signature of cytokines and angiogenic factors (CAFs) defines a clinically distinct subgroup of gastric cancer. *Gastric Cancer* 2015; Epub ahead of print [PMID: 26681196 DOI: 10.3892/mmr.2014.1961]

95 **Ye XL**, Zhao YR, Weng GB, Chen YC, Wei XN, Shao JP, Ji H. IL-33-induced JNK pathway activation confers gastric cancer chemotherapy resistance. *Oncol Rep* 2015; **33**: 2746-2752 [PMID: 25846650 DOI: 10.3892/or.2015.3898]

96 **Yang Z**, Guo L, Liu D, Sun L, Chen H, Deng Q, Liu Y, Yu M, Ma Y, Guo N, Shi M. Acquisition of resistance to trastuzumab in gastric cancer cells is associated with activation of IL-6/STAT3/Jagged-1/Notch positive feedback loop. *Oncotarget* 2015; **6**: 5072-5087 [PMID: 25669984]

97 **Kwon OH**, Kim JH, Kim SY, Kim YS. TWEAK/Fn14 signaling mediates gastric cancer cell resistance to 5-fluorouracil via NF-κB activation. *Int J Oncol* 2014; **44**: 583-590 [PMID: 24337061 DOI: 10.3892/ijo.2013.2211]

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

**L-Editor: E-Editor:**