Chapter 8
Molecular Signaling Pathways Involved in Gastric Cancer Chemoresistance

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Abstract Gastric cancer (GC) is the third most frequent cause of cancer-related deaths worldwide. The Molecular Mechanism of pathogenesis in GC is still unknown and unclear due to the Chemoresistance. Chemotherapy still remains only a single treatment for GC patients. Among those patients, most are becoming resisting to chemotherapeutic agents, nowadays chemoresistance causes recurrence and is a major challenge in the treatment of cancer because of the deregulations of numerous signaling pathways such as a tumor suppressor gene signaling, PI3K/Akt signaling, NF-κB signaling, Wnt/β-catenin signaling, mitogen-activated protein kinase (MAPK), Hedgehog signaling, Hippo signaling, Notch signaling pathways, and epidermal growth factor receptor (EGFR) have been found in GC. Epithelial-mesenchymal transition (EMT), as a major process during embryogenesis and tumor genesis, as well as is playing a vital role in chemoresistance of GC. In this chapter we summarize important molecular pathway aspects of multi-drug resistance (MDR). It is crucial for the identification of the new drug target, and combination therapy to clarify these complex molecular signaling mechanisms.

Keywords Gastric cancer · Chemoresistance

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Abbreviations

5-FU	Fluorouracil
Apa	Apatinib
ATM	Ataxia-telangiectasia mutated
BAD	Bcl-2-associated death promoter protein
CCL2	chemokine C-C motif ligand 2
CDDP	Cisplatin
DARPP-32	Dopamine and adenosine 3′, 5′-cyclic monophosphate-regulated phosphoprotein, Mr. 32000
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
GC	Gastric cancer
HMMR	Hyaluronan-mediated motility receptor
KRAS	Kirsten-Ras
LOH	Loss of heterozygosity
LRIG1	Leucine-rich repeats and immunoglobulin-like domains 1
MAPK	Mitogen-activated protein kinase
MDR	Multidrug resistance
MSC	Mesenchymal stem cell
MST1	Mammalian ste20-like kinase 1
NF-κB	Nuclear factor-kappa B
PI3K/Akt	Phosphoinositide-3-kinase–protein kinase B
TGI	tumor growth inhibition
Tzb	trastuzumab
VEGF	Vascular endothelial growth factor

8.1 Introduction

Remarkable progress has been made on the development and progression of human gastric cancer (GC) over the past decade. Gastric cancer represents the third leading cause of cancer deaths worldwide (Sitarz et al. 2018). The incidence rates of GC vary in different regions, with a higher incidence in Eastern Asia, European and South American countries and a lower incidence in North America and some parts of Africa (Marques-Lespier et al. 2016; Torre et al. 2016). In the management of unresectable tumors, several chemotherapeutic strategies have been used to relieve symptoms, to decrease the risk of recurrence and distant metastasis (Hamamoto 2015; Liu et al. 2016; Shin et al. 2016). The 5-year overall survival (OS) rate varies from 20% to 35% in these patients (Chon et al. 2017; Kuo et al. 2014). chemoresistance is a major hindrance to effective and successful cancer treatment

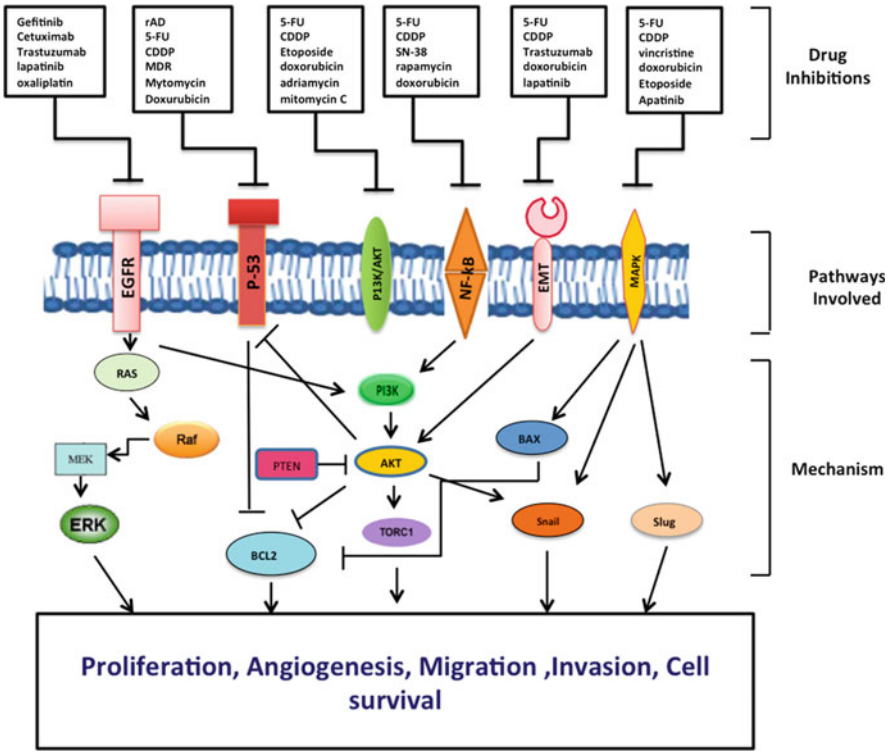

Fig. 8.1 Molecular mechanism of chemotherapeutic drugs involved in gastric cancer chemoresistance

in various cases. There are many reasons that lead to the failure of cancer chemotherapy (Fig. 8.1 and Table 8.1). Several lines of evidence report the involvement of tumor microenvironment (TME), Hedgehog (Hh), p53 oncogene, phosphatidylinositol-3 kinase (PI3K)/Akt, Notch signaling, mitogen-activated protein kinase (MAPK), Hippo signaling and WNT signaling pathways play role in GC chemoresistance (Gao et al. 2018; Martin et al. 2013). Hence, it is essential to understand its molecular mechanisms to identify a novel therapeutic target for cancer cell invasiveness and metastasis suppression. In this chapter, we summarized the major molecular signaling pathways that are involved in chemoresistance of GC.

8.2 Oncogenes p53

The p53 is one of the most well-known tumor suppressor genes involved in various important processes such as apoptosis, cell cycle regulation, and DNA repair. Hence p53 is also called as "guardian of the genome (Lane 1992). It has been observed that

Table 8.1 Summary of molecular signaling pathways and chemotherapeutic drugs associated with gastric cancer chemoresistance

Target pathways	Explanation	Chemo-drugs	Expression level	Reference
Tumor suppressor gene (P53)	Drug exposure increases mutant p53 levels by a translational mechanism	5-FU, Mytomycin, Cis-diclorodiamine platinum	Up-regulation	(Nabeya et al. 1995)
	Mutation of the p53 gene with increased overexpression of the Bcl-2 protein	CDDP	Up-regulation	(Ikeguchi et al. 1997)
		rAD	Up-regulation	(Chen et al. 2011)
	miR-27b up-regulation leads to increased miR-508-5p expression, mediated by CCNG1 and P53	MDR	Up-regulation	(Shang et al. 2016)
	Mutation of the p53 gene inhibits apoptosis	5-FU,CDDP	Up-regulation	(Matsuhashi et al. 2005)
	miR-19a/b suppressed drug-induced apoptosis by regulating Bcl-2 and Bax	Doxorubicin	Up-regulation	(Wang et al. 2013a)
EGFR	Up-regulated integrin beta4 expression inhibited apoptosis, and enhanced resistance	Gefitinib	Up-regulation	(Huafeng et al. 2018)
	Overexpression of EGFR and low levels of receptor activation, MET activation and mutations of KRAS and CDH1 was associated with resistance	Cetuximab	Up-regulation	(Heindl et al. 2012)
	Overexpression of DARPP-32, promote interaction between EGFR and ERBB3 and blocked gefitinib-induced apoptosis	Gefitinib	Up-regulation	(Zhu et al. 2011)
	HER2-positive cells prevent cell apoptosis via autophagic flux inhibition through mTOR pathways	Trastuzumab	Up-regulation	(Ye et al. 2018)
	Higher PD-L1 expression and dMMR and HER2 status indicate drug resistance	Trastuzumab	Up-regulation	(Wang et al. 2018)
	Up-regulation of HER2 and MET and Downregulation of FOXO1gene increased resistance	Apatinib	Up-regulation	(Park et al. 2018)
	Up-regulation of ATXN2L was responsible for intrinsic and acquired chemoresistance	Oxaliplatin	Up-regulation	(Lin et al. 2019)

(continued)

Table 8.1 (continued)

Target pathways	Explanation	Chemo-drugs	Expression level	Reference
P13K/AKT	Wortmannin promotes caspase-3, caspase-9 activation, and poly ADP-ribose polymerase cleavage and increased drug resistance	Etoposide, doxorubicin	Up-regulation	(Yu et al. 2008)
	AKT activation and LOH of PTEN enhanced chemoresistance	5-FU, adriamycin, mitomycin C and CDDP	Up-regulation	(Oki et al. 2005)
	pAkt- and p53-positive tumors, enhanced chemoresistance	5-FU	Down-regulation of AKT and up-regulation of p53	(Murakami et al. 2007)
	Down-regulation of PTEN and PIK3CA gene could activate the PI3-kinase/AKT signaling pathway of chemoresistance	CDDP	Up-regulation	(Byun et al. 2003)
	Suppression of the expression of p53 and promoting the expression of c-Myc enhanced chemoresistance	Etoposide	Up-regulation	(Liu et al. 2006)
	Up-regulation of Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway promotes drug resistance	CDDP	Up-regulation	(Zhang et al. 2013)
	P-AKT might be up-regulated of Bcl-2, and down-regulate of Bax protein and promote drug resistance	MDR	Up-regulation	(Han et al. 2007)
MAPK	Overexpression of the MDR1gene promotes resistance to P-gp-related drug and P-gp-unrelated drugs	Vincristine	Up-regulation	(Guo et al. 2008)
	Overexpression of the Bax and decrease Bcl-2 expression involved in drug resistance	Doxorubicin	Up-regulation	(Tan et al. 2014)
	Upregulation of miRNA-16 promotes drug resistance	5-FU, Etoposide	Up-regulation	(Wang et al. 2013b)
	High expression of DUSP1 may be responsible for drug resistance	Apatinib	Up-regulation	(Teng et al. 2018)
	Up-regulated miR-135b was regulating MST1 and increased drug resistance	CDDP	Up-regulation	(Zhou and Chen 2019)
	Down-regulation of miR-206 is associated with drug resistance	CDDP	Up-regulation	(Chen et al. 2019)

(continued)

Table 8.1 (continued)

Target pathways	Explanation	Chemo-drugs	Expression level	Reference
NF-kB	Up-regulation of PTEN expression via CBF-1 binding enhanced drug resistance	Doxorubicin	Up-regulation	(Zhou et al. 2013)
	The NF—kB pathway is activated in response to chemotherapy	5-FU, SN-38	Up-regulation	(Camp et al. 2004)
	ERas induces chemoresistance to CPT-11 via activation of the signaling pathway	Rapamycin	Up-regulation	(Kubota et al. 2011)
	Overexpression of APRIL decreased the efficacy of chemo drugs	CDDP	Up-regulation	(Zhi et al. 2015)
	Up-regulation of IL-8 increased ABCB1 expression which promotes chemoresistance	CDDP	Up-regulation	(Zhai et al. 2019)
EMT	HMMR activates the TGF-beta/Smad2 and promotes chemoresistance	5-FU,	Up-regulation	(Zhang et al. 2019)
	Testican-1 mediated drug-resistance in HER2 positive cells	Apatinib	Up-regulation	(Kim et al. 2014)
	Overexpression of the HER2/snail positive cell increased chemoresistance	CDDP	Up-regulation	(Huang et al. 2016)
	Up-regulation of eif5a2's expression enhanced the chemoresistance	CDDP	Up-regulation	(Sun et al. 2018a)
	Up-regulation of HER4, p-HER4, YAP1, and Vimentin were associated in chemoresistance	Trastuzumab	Up-regulation	(Shi et al. 2018)
	Up-regulation of DUSP4 promotes chemoresistance	Doxorubicin	Up-regulation	(Kang et al. 2017)
	Down-regulation of miR-30a promotes chemoresistance	CDDP	Up-regulation	(Wang et al. 2016)

p53 universally mutated in all categories of cancer including GC. The cyclin-dependent kinase inhibitor P21 is a major target of p53 activity and these are associated with cell cycle arrest and tumor growth inhibition (TGI). About 60% of GC tissues showed a reduction in P21 expression and it significantly correlates with tumor metastasis, invasiveness and poor prognosis (Gamboa-Dominguez et al. 2007).

Further, p53 gene mutations rate was found to be 0–77% in GC (Fenoglio-Preiser et al. 2003). Moreover, the function of p53 alterations causes by loss of heterozygosity (LOH) including a high incidence of p53 mutations and infrequently by DNA methylation. Several mutations may exist in a one tumor causing in the heterogeneity of the p53 position, high-expression of the p53 protein, and the low level of p53 function which are initial events in GC (Bellini et al. 2012). Although the multifaceted relationship between p53 and chemoresistance in GC has been studied for several years, the outcomes are inconsistent. Currently, an epidemiological study was conducted to explain the associations between p53 mutations and the response to chemotherapy. The results indicated that p53 might be a good prognostic biomarker for early response to chemotherapy in GC (Xu et al. 2014).

A study has examined in GC cell lines for p53 mutational status and the results indicate that wild-type p53 protein expression increase during treatment with 5-fluorouracil (5-FU), mitomycin C, and cis-dichlorodiammin-e platinum (CDDP), In contrast, these consequences show that the mutation of p53 is predictive of chemosensitivity in GC (Nabeya et al. 1995). p53 induced apoptosis has been confirmed in GC cells by down-regulating of Bcl-2 protein and the up-regulating the expression of mutated p53 genes in MKN-74 cells after CDDP treatment (Ikeguchi et al. 1997). Additionally, Chen et al. showed that treatment with rAd-p53 significantly increased the sensitivity of the GC to chemotherapy by enhancing Bax expression and inhibits apoptosis (Chen et al. 2011). A study reported that miR-27b plays a major role in tumor development to chemotherapy in vitro and in vivo. Interestingly, up-regulation of miR-27b leads to enhanced miR-508-5p expression, mediated by mutant P53 in GC-associated MDR (Shang et al. 2016). Matsuhashi et al. demonstrate that combined administration of 5-FU and CDDP, induce apoptosis in MKN45, but not in MKN28 cell line these data indicated that the mutated p53 may deliver confirmation of the idea that p53 expression is related to MDR in GC (Matsuhashi et al. 2005). Hamada et al. analyzed and detected 4 GC patients with p53 mutations out of 24 patients with other cancer by immunehistochemical staining and found that p53-inducible WAF1/CIP1 protein in wild type p53 expression but not in mutant-p53 these results suggest that mutations in p53 are associated with lower response or chemosensitivity in GC (Hamada et al. 1996). In addition, it shows that microRNAs are involved in the up-regulation of MDR1 and overexpression of miR-19a/b confers resistance to doxorubicin on GC cells and decreasing the expression of Bcl-2 and Bax gene (Wang et al. 2013a).

8.3 Growth Factor Receptor and Signaling

Epidermal growth factor receptor (EGFR) is a transmembrane protein. Up-regulation of EGFR has been reported in 9–30% of GC cases (Terashima et al. 2012). It is a kind of glycoprotein receptor with HER family of tyrosine kinase activity, When the EGFR extracellular domain binds to its ligands proteins such as transforming growth factor-α (TGF-α), it promotes dimer formation with other EGFR family members

which leads to high expression of EGFR and activate PI3K/Akt/mTOR, JAK/stat3, SOS/Grb2/Ras, and src/FAK/ROS pathways, as well as involved in differentiation, proliferation adhesion and metastasis in GC (Lee et al. 2015; Roskoski 2014).

Further, overexpression of EGFR can trigger STAT3 and NFκB, which leads to chemoresistance and poor prognosis in GC. Recently, Huafeng et al. identified that the up-regulation of integrin β4 expression was promoted gefitinib resistance and proliferation by inhibiting apoptosis and showed a negative correlation between integrin β4 and EGFR in GC patients (Huafeng et al. 2018).

An in vitro study on cell lines showed High EGFR expression with MET activation and Kirsten-Ras (KRAS) and CDH1 gene mutations was positively associated with cetuximab resistance in GC (Heindl et al. 2012). To complement this result one study also showed that, activation of *KRAS* mutation promotes cetuximab resistance in GC cell line (Kneissl et al. 2012). Zhu et al. reported that gefitinib resistance was associated with up-regulation of Dopamine and adenosine 3′,5′-cyclic monophosphate-regulated phosphoprotein, Mr 32,000 (DARPP-32) through EGFR mediated phosphatidylinositol-3-kinase–AKT signaling pathways in GC cells lines (Zhu et al. 2011).

Furthermore, Ye et al. indicated that autophagy plays a vital role in the resistance of HER2-positive in NCI-N87 cell lines to trastuzumab (Tzb) and showed that Tzb drug prevents cell apoptosis by autophagic flux inhibition. Which activate the Akt/mTOR pathway in GC (Ye et al. 2018). Additionally, Wang et al. found that patients with Tzb resistance existing high HER2 somatic copy number alterations (SCNA) during development. The PIK3CA mutations were significantly advanced in patients with innate resistance, compared with standard, as well as NF1 mutations also contributed a role in Tzb resistance in GC (Wang et al. 2018). Moreover, a current study showed that FOXO1 gene works as connective linker among HER2 and MET signaling pathways and play a key role in the regulation of the Apatinib resistance in HER2-positive GC cells. These findings suggest a novel strategy for treatment to overcome apatinib resistance in GC patients (Park et al. 2018). Very recent a study demonstrates that EGFR can stimulate ATXN2L gene expression and promotes cell invasiveness which leads to oxaliplatin resistance. This data indicates poor prognosis for overall survival and recurrence in GC tissue (Lin et al. 2019). Another study observed that Leucine-rich repeats and immunoglobulin-like domains 1 (LRIG1) was up-regulated in chemosensitive GC MDR cell lines via EGFR-mediated PI3K/AKT and MAPK/ERK signaling pathways and decreased expression of LRIG1 (Zhou et al. 2018).

8.4 PI3K/AKT Signaling Pathway Activation

The PI3K/Akt is a serine/threonine-specific kinase protein work as a key regulator of cell growth, proliferation, migration, and survival; it has been observed that is frequently active in GC. Overexpression of PIK3CA is frequently detected with a poor outcome in GC (Tsujitani et al. 2012) the triggering of TKI activates PI3K,

which initiates AKT. Activated Akt can phosphorylate various Bcl-2-associated death promoter protein (BAD) on ser136 for the detach from Bcl-X/Bcl-2 gene family and overcome apoptosis initiating signals of BAD. Mutations in PIK3CA lead to activation of the PI3K signaling activity reported in GC confirmed by microarray analysis (Li et al. 2005). It has been reported the aberrant activation of the Akt also able to stimulate NFkB up-regulation, which helps in the transcription of pro-survival genes and overexpression of Akt1 outcomes in drug resistance of GC cells to chemotherapeutic agents. Nam et al. found that high expression of p-AKT and AKT was 78% and 74% in GC, respectively (Nam et al. 2003). Yu et al. observations have proven that high expression and phosphorylation of Akt could be deactivated by etoposide, doxorubicin and wortmannin and could increase the resistance of GC cells to chemotherapy through PI3K/Akt signaling pathway (Yu et al. 2008).

Moreover, a study has revealed that activated AKT and LOH of PTEN plays a major role in broad-spectrum resistance to adriamycin, mitomycin C, cis-platinum and 5-FU chemo drugs, mediated by AKT/PI3K pathways in GC patients (Oki et al. 2005). Another report also compliments this result adding with fluorouracil resistance treatment (Murakami et al. 2007). and Down-regulation of PTEN can lead to CDDP resistance, in GC cells (Byun et al. 2003) Liu et al. demonstrated that Etoposide can stimulate activation of the PI3K/AKT signaling pathway, which reduced the chemo drugs sensitivity of SGC7901 and BGC823 GC cell lines (Liu et al. 2006) Further, in one study, demonstrate that the overexpression of AKT at the molecular and cellular level is associated with CDDP resistance through the JAK2/STAT3 pathway and decreased the chemosensitivity of GC cells in vitro and in vivo (Zhang et al. 2013). And the down-regulation of AKT1 significantly increased cell sensitivity towards AGS cells to adriamycin, cisplatin, 5-fluorouracil, and vincristine chemotherapeutic drugs (Han et al. 2006).

It has been noticed that NF-kB work as a chemotherapeutic inducer of AKT activation, degradation, and phosphorylation also involved in the chemoresistance of GC cells (Yu et al. 2010). Recently Song et al. found that loss of CD133 stem cell biomarker significantly increased the growth inhibition of chemo agents and knock-down of CD133 significantly reduced the PI3K activity in the GC (Song et al. 2018). However, the PI3K/AKT signaling pathway plays a crucial role in drug resistance, the molecular mechanism of PI3K/AKT activation in chemoresistance is not completely understood. According to a study, Survivin plays an important role in downstream of AKT. higher levels of survivin and p-AKT have been detected In CDDP-resistant GC (Sun et al. 2014) Additionally, the overexpression of p-AKT could be responsible for MDR in AGS GC cell lines by the up-regulation of BCL-2 expression (Han et al. 2007).

8.5 Mitogen-Activated Protein Kinase Signaling Pathway

The mitogen-activated protein kinase (MAPK) including p38 and JNK kinase signaling pathway responds to extracellular stimulation and broadly expressed in eukaryotic organisms (Johnson and Lapadat 2002). which plays a crucial role in several biological processes, such as cell proliferation, differentiation, and survival of tumor cells. Deregulation of the MAPK signaling is associated with the progression of GC (Yang and Huang 2015). Besides, these numerous studies have confirmed that the MAPK pathway is also involved in chemotherapy resistance in GC. According to Atmaca et al. phosphorylated MAPK was positive in 59.6% of Cases with metastatic GC and Overall survival was found 8.5 months also, it has been observed that the expression of p-MAPK in primary and metastatic tumors was similar. These results directed that p-MAPK expression may be a probable predictive marker in metastatic GC who is ongoing treatment with chemotherapy (Atmaca et al. 2011). Further, the overexpression of the p38-MAPK signaling pathway was found in vincristine-resistant SGC7901/VCR GC cell lines and to be responsible for the MDR (Guo et al. 2008). Tan et al. demonstrates that the up-regulation of p38 MAPK pathway was involved in doxorubicin resistance in GC cells (SGC7901, BGC823) and xenograft model besides inhibition of p38 MAPK increased GC cell sensitivity to doxorubicin through the induction of the BAX and decrease in BCL-2 expression (Tan et al. 2014). Wang et al. found that etoposide and 5-FU could be activated miRNA-16 expression in vitro and in vivo, and the overexpression of miRNA-16 is mediated by p38MAPK in GC (Wang et al. 2013b). Recently, Teng, et al. was shown, that the expression of DUSP1 gene was significantly higher in the early stages of GC and associated with apatinib (Apa) resistance in GC cells through activation of MAPK signaling pathways in vitro (Teng et al. 2018).

Another current study reported that mammalian ste20-like kinase 1 (MST1) play a vital role in the progression of GC and the reduced sensitivity to CDDP in MKN45 cell lines. Down-regulation of miR-135b resulting in the reverse of CDDP resistance and increases the cells death via activation of MST1-mediated MAPK signaling pathway (Zhou and Chen 2019). along with, Chen et al. found that The down-regulation of miR206 is significantly associated with CDDP resistance of GC cells via induction of MAPK3 pathway (Chen et al. 2019).

8.6 NF-κB Signaling Pathways

Nuclear factor kappa B (NF-κB) constitutes a family of transcription factors and regulated by polyubiquitination, proteasomal degradation, and phosphorylation, by IκB protein. Which form homo and heterodimers and responsible for up-regulation or suppression of many genes involved in inflammation, cell proliferation, cell survival and immunity (Neumann and Naumann 2007). The activation of NF-κB RelA homology domain driven cytokines to include IL-1, IL-6, IL-8, MCP-1, TNF,

pro- and anti-apoptotic factors. Especially, deregulation of NF-κB signaling pathway promotes tumor genesis which Associated with poor prognosis of GC and chemoresistance (Kinoshita et al. 2010; Kwon et al. 2012; Maeda and Omata 2008). Zhou et al. revealed that AKT1 expression was induced by doxorubicin. The activation of AKT can increase the binding of NF-kB on Notch1 promoter. Further up-regulation of PTEN by Notch-activated transcription factor (CBF1) in vitro and in vivo results, suggested that an AKT1/NF-kB/PTEN play an important role in the development of chemoresistance in GC (Zhou et al. 2013). Camp et al. found that NF-kB is activated in NCI-N87 and AGS human GC cells in response to 5-FU and SN-38 chemotherapeutic drugs, and May outcome in inducible chemoresistance (Camp et al. 2004). A another study demonstrated that ERas-overexpressing clones were significantly more resistant to CPT-11 after treatment of rapamycin than the control in GCIY cells via activation of NF-κB/mTOR pathway (Kubota et al. 2011) A recent study reported that conditioned medium (CM) made by the metabolism of SGC-7901 GC cell lines increased drug resistance by activating the ataxia-telangiectasia mutated (ATM) and NF-κB pathways in GC cells (Zhuang et al. 2018) Zhi et al. found that Up-regulation of APRIL in AGS cells significantly decreased the efficacy of CDDP in vitro and in vivo and data showed that NF-κB pathway involved in APRIL-mediated chemo-resistance in GC patients (Zhi et al. 2015). Further, a study revealed that IL-8 was overexpressed in GC drug-resistant patients, and increased the IC50 of CDDP in AGS cells, located in cancer-associated fibroblasts (CAFs). Instantaneously, IL-8 therapeutic enriched the expression of PI3K, p-AKT, p-IKb, p-p65 and ABCB1, besides promotes chemoresistance through NF-κB activation and up-regulation of ABCB1 (Zhai et al. 2019). In Additional, Xu et al. reported that drug-resistant GC cells secrete more chemokine C-C motif ligand 2 (CCL2) than drug-sensitive cells and decreased the drug-induced cytotoxicity by inhibiting autophagy and increase SQSTM1 expression. Besides, these enhanced the expression of SQSTM1 in turn, activated CCL2 transcription via the NF-κB signal pathway, demonstrating as a positive feedback drug resistance (Xu et al. 2018). Hypoxia is another well-recognized common feature in tumor biology to be a key point of treatment resistance and poor prognosis in several cancer patients. Hypoxia leads to the expression of many genetic factors that are involved in tumor progression and metastasis in GC (Griffiths et al. 2005). HIF-1α can induce the vascular endothelial growth factor (VEGF) expression and inflammatory state through NF-kB signaling pathway which leads to the suppression of p53 and promotes 5-FU and CDDP chemoresistant in human GC cells (Rohwer et al. 2010). Nakamura et al. has been reported that HIF-1α leads to drug resistance against adjuvant chemotherapy using 5-FU in advance gastric tumor patients (Nakamura et al. 2009). overexpression of HIF-1α increases the expression of Bcl-2 and reduces the expression of Bax protein outlining hypoxia-induced drug resistance in GC (Liu et al. 2008).

8.7 EMT

Epithelial-mesenchymal transition (EMT) is a multistage reprogramming process play a vital role in the development of homogenous adhesion that is essential for embryonic expansion and fibrotic disease (Peng et al. 2014). During EMT progression, there is a loose cell polarity in epithelial cell junctions and increase invasive properties of the mesenchymal stem cell (MSCs). Consequently, the expression of epithelial marker such as E-cadherin showed down-regulation and activates β-catenin, which translocate into the nucleus and modulates the expression of VEGF, CD44, cyclin D1kinase, and c-Myc which leads to tumor initiation and progression. it has been observed that the expression of mesenchymal markers such as Snail, Slug, Vimentin, ZEB1, ZEB2 is up-regulated in tumor cells (Thiery et al. 2009).

However, the ability to self-renewal, an overexpression of Drug resistance genes, have shown that the EMT is a major molecular mechanism linked with metastasis and provide resistance to chemotherapy (Mitra et al. 2015). Recent studies have proved that hyaluronan-mediated motility receptor (HMMR) was up-regulated in 5-Fu resistant GC cell line. Further, biopsies sample observed that HMMR increased the cancer stem cell (CSCs) properties and resistance to chemotherapy via TGF-beta/Smad2-induced EMT in GC (Zhang et al. 2019). Kim et al. described the Testican-1 are responsible for EMT mediated signaling and confers acquired resistance to apatinib in HER2-positive gastric cancer in in-vitro (Kim et al. 2014).

Similarly, Huang et al. found that up-regulation of HER2/Snail double-positive patients had poor survival and significantly associated with CDDP-resistant in GC cells mediated by EMT (Huang et al. 2016). Eukaryotic translation initiation factor 5A2 (eIF5A2) is an essential tumor-promoting function in GC. One report showed that the Silencing of eIF5A2 factor enhanced the sensitivity of GC cells to cisplatin by mediating EMT (Sun et al. 2018b). A current study found that phosphorylated p-HER4, HER4, YAP1, and Vimentin were significantly higher and HER2 and E-cadherin were found down-regulated in response to the trastuzumab in vivo. These results revealed that the major role of the HER4-YAP1 in trastuzumab resistance of HER2-positive GC cells via induction of EMT (Shi et al. 2018). Kang et al. demonstrated that up-regulation of DUSP4 can enhance doxorubicin resistance by stimulating EMT in GC cells (Kang et al. 2017).

A study Report proposed that depletion of TAZ (transcriptional co-activator) caused partial Transition of EMT to MET in CDDP resistant GC cells, which are negatively regulated by the Hippo pathway (Ge et al. 2017). Wang et al. also showed that the chemoresistance to cisplatin-induced EMT in human GC cells (Wang et al. 2016). Additionally, has been observed that Doxorubicin is able to induce EMT in GC patients through inhibition of the β-catenin signaling pathway by indomethacin and inhibition of p300 in BGC-823 GC cell (Han et al. 2013; Han et al. 2014). Moreover, Fas belongs to a member of the TNF family, which stimulate tumor cell motility inducing EMT, and support metastasis formation in GC. down-regulation of Snail and Twist expression significantly decreased Fas-induced motility, as well as

the use of oxaliplatin chemo drug prompt to induce EMT moderately resulting in chemo-resistant through Fas signaling pathway (Zheng et al. 2013).

8.8 Conclusion

The chemoresistance of tumor cells to chemotherapy occurs from a reduction in drug availability and induction of several oncogenic signaling pathways. Due to the cell specificity to chemoresistance. Major chemoresistance-related proteins are localized in the cell membrane; these proteins are complex and highly versatile in various events, including apoptosis, proliferation, autophagy, and EMT. Now it is essential for the cancer patients receiving targeted combine therapy to increase therapeutic efficacy and reduced tissue toxicity. This chapter may deliver a further understanding of molecular signaling network in Gastric cancer chemoresistance, which facilitates the establishment of novel therapeutic targets and potential chemo sensitive biomarkers to decrease the cancer recurrence and improve the patient lifespan.

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