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Micro RNA facilitated chemoresistance in gastric cancer: a novel biomarkers and potential therapeutics

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ABSTRACT

Introduction: In spite of the substantial advances in clinical practice, Gastric cancer (GC) remains the third leading cause of cancer death worldwide. The incidence of drug resistance remains a hindrance to effective treatment for GC. Although the molecular mechanisms of chemoresistance have broadly studied, the gene regulation and expression mechanisms of miRNA have not entirely understood.

Methods: Online databases of PubMed, Scopus, Google Scholar, and Embase databases were searched to retrieve relevant publications. The following keywords were used: MicroRNA, Non-coding RNA, miRNA, Gastric cancer, drug resistance, and chemoresistance.

Results: miRNAs play a pivotal role in the initiation, progression of tumor and metastasis, as well as in the development of pathways mediating resistance to chemotherapy in GC. Unluckily, to date, there is no consistent, reliable biomarker available to predict the response of chemotherapy before the start of the treatment.

Discussion: In this review, we would like to provide an overview of the miRNAs and miRNA facilitated chemoresistance machinery in GC to develop a personalized treatment to overcome GC drug resistance.

1. Introduction

Gastric cancer (GC) remains the fourth most common cancer worldwide. Recent data indicate that one million new cases of GC are diagnosed each year in globally [1]. The average incidence of GC is extremely variable by region and is more commonly diagnosed in developed countries. The incidence rate is highest in Eastern (32.1/100,000 males and 13.2 females) and Central Asian populations [2]. At present, radiotherapy, combinational chemotherapy, and surgery are the main therapeutic options for GC. However, in many patients these treatments are not successful due to the resistance of chemotherapeutic Drugs [3]. The tumor intrinsic (preexistent) or acquired (drugs induced), mechanisms of resistance, makes a major obstacle to develop effective cancer therapies. In recent years, due to endoscopy and surgery in an early stage of GC, the overall 5-year mortality rate was expressively reduced up to 67%, while in advanced GC it remains only 50% [4]. In advanced GC, lymph node metastasis, peritoneal dissemination, and rectal metastasis via hematogenous accelerate the cell proliferation, migration, invasion leading to recurrence of cancer cells and mortality with several molecular pathways [5,6].

MicroRNA (miRNAs) are 18–25 bp short noncoding RNAs that bind to the 3′- untranslated region (UTR), specifically in the MRE sequence (miRNA recognition element) and inhibit the gene expression [7]. Emerging evidence demonstrated that miRNAs play a pivotal role in the progression of tumor and metastasis, as well as chemoresistance in GC [8–12]. In this review, we will emphasized on the role of miRNA mediated chemoresistance mechanisms in GC and provide novel insights in the field of miRNA for GC diagnosis and prognosis.

2. The biological significance of miRNA

miRNAs are highly conserved endogenous small noncoding sequences which are involved in the normal functioning of eukaryotic cells. Lee et al. discovered the first miRNA lin-4 in the 3′ untranslated region (UTR) of *C. elegans* [13]. miRNA genes are transcribed by RNA polymerase (II and III) from non-coding (introns), coding (exons) regions, generating initial precursors that undergo a series of cleavage events by the Drosha/DGCR8. pri-miRNA also regulated by several transcription factors (TFs), and finally, pri-miRNA transcribed as mature miRNA in the cytoplasm [14,15]. Further, it is predicted that single

miRNAs can combine with many different mRNAs and may regulate the expression of > 60% protein-coding genes in human genome [16]. Concerning the miRNA's biological relevance, these small molecules are regulatory elements in various biological processes, including cell differentiation, proliferation, and apoptosis and The miRNA regulate the multiple genes involved in cancer progression and metastasis [17,18].

3. miRNA and drug resistance in GC

To date, more than 2000 miRNAs have been identified, and some of them are significantly associated with tumorigenesis, cancer invasion, metastasis and also apoptosis in GC [19]. A recent study demonstrated that one single miRNA could act as an oncogenic miRNA as well as tumor suppressor miRNAs which seem to have a significant role in drug resistance [20]. The relationship between miRNA expression and sensitivity of GC to chemotherapeutic drugs is studied extensively. A recent study reported that the miR-551b-3p directly binds to the intronic region of dysbindin mRNA and negatively regulates the expression and involved in Platinum resistance in GC cells [21]. Further, decreased miR-122 expression is directly involved in the induction of cisplatin (CDDP) resistance by increasing excision repair cross-complementing 1 (ERCC1) expression [22]. Xi et al. showed that metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), which potentiates autophagy-associated CDDP resistance by regulating the miR-30b in GC [23]. Furthermore, Wang et al. Showed that overexpression of miR-574-3p reduced the migratory and invasive properties of the GC cells and inhibit the EMT and enhanced cisplatin sensitivity in GC cells by suppressing in vitro and in vivo [24]. Recentaly, Tao et al revealed that miR-92a contributes role in cell proliferation, apoptosis and doxorubicin chemosensitivity in GC cells, and suggests a potential therapeutic strategy for the treatment of GC [25].

Table 1 & Figure 1 documents the features of 39 miRNAs that regulate the chemoresistance mechanisms in GC. Among them, 29 miRNA were down-regulated and significantly decreased sensitivity to chemo drugs, and 10 are up-regulated in different resistant pathways.

4. Prognostic prediction and therapeutic response of GC

The prognosis of GC remains poor due to the slow progress in the development of diagnostic and therapeutic machinery. Tumor-node-metastasis staging (TNM staging) system is the most widely used independent predictor of survival for GC individuals [63]. On the other hand, TNM staging is alone not enough to predict the prognosis of GC in diverse stages [64]. Therefore, it is very crucial to identify key factors that predict the overall survival and response rate to the existing therapeutic options. However, GC linked to tumor extension and nodal involvement beyond the gastric wall; It may provide some vital information to predict GC [65]. The overexpression of miR-93 is associated with reduced cellular response to transforming growth factor (TGF-β) by influencing the synthesis of p21, a well known apoptotic protein [66]. Overexpression of miR-93 was strongly associated with GC to predict poor survival rate. Apart from this, altered expression of miR-125 showed as a significant prognostic factor for survival of GC patients [67,68]. Zhang et al. reported that high expression of miR-21-5p is associated with poor overall survival (OS) and disease-free survival (DFS) in GC. Further, they found that overexpression of miR-200c-3p, miR-222-3p might also influence the prognosis of GC [69].

Down-regulation of miR-376a may contribute to the in tumorigenesis and progression of GC and act as a potential therapeutic candidate and help to predict prognosis of GC [70]. Notably, the identification of miRNAs as a prognostic factor of GC will not only aid in predicting the prognosis, but also help to develop new therapeutic targets in the future. Therefore, further analysis of miRNAs is very crucial in GC therapy.

5. miRNAs in the identification of gastric cancer

Despite accumulating data on genetic and epigenetic events in GC, the lack of adequate noninvasive tools for early identification of GC remains the most significant challenge. Currently, serum tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen 724 (CA724) and carbohydrate antigen 199 (CA199) are in use for detecting GC. However, serum tumor markers have poor sensitivity and less specificity [71]. Thus, it is an urgent requirement to discover novel diagnostic agents to detect the GC. Since the last decade, miRNAs are gathering a lot of scientific attention and opening new windows to find out a centered way to detect GC in early stage. From this perspective, in silico research identified 14 miRNAs of which 3 miRNAs (miR-211, let-7b, and miR-708) were first time reported and could be used as a novel potential biomarker in GC after further clinical validation [72]. An experimental data of Korean cohort distinguished miR-24 as stage 1 and stage 2 diagnostic markers in GC patients. Shin and colleagues showed that miR-627, miR-629 and miR-652 were significantly up-regulated in GC and play a role as a crucial noninvasive diagnostic marker [73]. Hwang et al. showed that dysregulation of miR-107,

Table 1. Compendium of MicroRNAs involved in gastric cancer drug resistance.

miRNA	Regulation	Involved Genes	Drug Target	Modal	References
miR-217	Down	EMT	PTPN14	*in-vitro*	[26]
miR-200bc/429	Down	BCL2, XIAP	VCR, CDDP, VP-16, ADR, 5-Fu	*in-vitro*	[27]
miR-181b	Down	BCL2	VCR, CDDP, 5-Fu, VP-16, ADR, MMC	*in-vitro*	[106]
miR-497	Down	BCL2, IGF1R, IRS1	VCR, CDDP, VP-16, ADR, 5-Fu	*in-vitro*	[107]
miR-503	Down	BCL2, IGF1	VCR, CDDP	*in-vitro*	[28]
miR-143	Down	BCL2, IGF1R, ERK5	CDDP, 5-Fu	*in-vitro*	[29]
miR-449a	Down	BCL2,CCDN1	CDDP	*in-vitro*	[30]
miR-15b	Down	BCL2	VCR, CDDP, VP-16, ADR, 5-Fu, MMC	*in-vitro*	[104]
miR-16	Down	BCL2	VCR, CDDP, VP-16, ADR, 5-Fu, MMC	*in-vitro*	[104]
miR-34a/b	Down	BCL2 NOTCH pathway, HMGA2	CDDP, DOX, DTX, GEM	*in-vitro*	[115]
miR-34c-5p	Down	MAPT	Paclitaxel	*in-vitro*	[31]
miR-204	Down	BCL2, TGFBR2- EMT	5-Fu, L-OHP	*in vitro* and *in vivo*	[32,33]
miR-19a	Down	CASC2	CDDP	*in vitro*	[34]
miR-1271	Down	IGF1R, IRS1, MTOR BCL2	CDDP	*in-vitro*	[35]
miR-103/107	Down	CAV1	DOX	*in vitro* and *in vivo*	[36]
miR-20a	Down	EGR2,CYLD	CDDP, Docetaxel	*in-vitro*	[37,38]
miR-145	Down	IRS1, BACT	5-Fu	*in vitro*	[39]
miR-508	Down	ABCB1, ZNRD1	VCR, CDDP, 5-Fu, ADR	*in vitro* and *in vivo*	[105]
miR-129-5p	Down	ABCB1, ABCC5, ABCG1	VCR, ADR, CDDP, 5-Fu	*in vitro* and *in vivo*	[40]
miR-218	Down	smoothened (SMO)	ADR, 5- Fu, L-OHP	*In-vitro*	[41]
miR-34c-5p	Down	MAPT	PTX	*in-vitro*	[31]
miR-125b	Down	MAPK, BAK1, WNT, P53 pathway	5-Fu	*in vitro*	[42]
miR-23b-3p	Down	ATG12, HMGB2	VCR, CDDP, 5-Fu	*in vitro* and *in vivo*	[43]
miR-939	Down	Raf/MEK/ERK pathway	5-Fu	*In-vitro* and *in-vivo*	[132]
miR-149	Down	FoxM1	CDDP	*in-vitro*	[44]
miR-501	Down	BLID, PI3K/AKT	Dox	*In-vitro* and *in-vivo*	[45,46]
miR 876-3p	Down	TMED3	CDDP	*in-vitro*	[47]
miR 613	Down	Sox9	CDDP	*in-vitro*	[48]
miR-320	Down	ERK, AKT	5-Fu	*in-vitro*	[49]
miR-633	Down	Foxo3a	CDDP	*In-vitro* and *in-vivo*	[50]
miR-16	UP	MAPK	VP-16,5-FU	*in vitro* and *in vivo*	[51]
miR-19a/b	UP	PTEN	CDDP, 5-Fu, ADR	*in vitro*	[100]
miR-106a	UP	E2F1, MTOR STAT3, PTEN,RUNX3	CDDP, 5-Fu, ADR	*in-vitro*	[52,53,101]
miR-21	UP	PTEN, ABCB1	CDDP, PTX, Trastuzumab	*in-vitro*	[54,55,102]
miR-20a	UP	NfKB/IB	CDDP	*in-vitro*	[38,56]
miR-223	UP	FBXW7	CDDP	*in-vitro*	[57]
miR-23a	UP	IRF1	PTX	*in-vitro*	[58]
miR-4516	UP	ING4	5-Fu	*in-vitro* and *in-vivo*	[59]
miR – 193a- 3	UP	Bcl-2, SRSF2	CDDP	*in-vitro*	[60,61]
miR-498	UP	BMI1	CDDP	*In-vitro* and *in-vivo*	[62]

ABCB1 (ATP-binding cassette, sub-family B, member 1), IGF1R (insulin-like growth factor 1 receptor), IRS1 (insulin receptor substrate 1), ZNRD1 (zinc ribbon domain-containing), PTEN (phosphatase and tension homolog), BCL2 (B-cell lymphoma 2), XIAP (X-linked inhibitor of apoptosis protein), RUNX3 (runt-related transcription factor 3), SMO (Smoothened), MAPT (microtubule associated protein tau), HMGA2 (high-mobility group AT-hook 2), IRF1 (interferon regulator factor 1); 2 VCR (vincristine), CDDP (cisplatin), ADR (adriamycin), VP-16 (etoposide), 5-Fu (5-fluoruracil), MMC (mitomycin C), DOX (doxorubicin), DTX (docetaxel), GEM (gemcitabine), PTX (paclitaxel), L-OHP (oxaliplatin); PI3K (phosphoinositide-3-kinase), ERK (extracellular-signal-regulated kinase), IRFI (Interferon Regulatory Factor 1), EGR (Early Growth Response), CAV (Caveolin), EMT (Eepithelial-mesenchymal transition) EGR2 (Early Growth Response-2), Fas-associated protein with death domain (FADD)

miR-300, miR-26a, and miR-375 in an early stages of GC [74]. The above evidences indicated that miRNAs are promising candidates serving as novel prognostic marker in the early stage of GC.

6. Invasion and miRNAs

Several studies demonstrated that dysregulation of miRNAs has been involved in various cancer progression mechanisms including invasion and metastasis. Recently, Kim et al. observed that overexpression of hsa-miR-421/hsa-miR-29b-1-5p in MKN-74 cells might play an essential role in the migration of GC and prevented the progression of GC [75]. Mei et al. showed that miR-1275 overexpression could suppress the invasion and metastasis of GC through targeting of JAZF1 [76]. Wang et al. noticed that up-regulation of Wnt7a suppressed the miR-127 expression and reversed the ability of GC cell migration and invasion [77]. Xu et al. demonstrated that speckle-type POZ protein (SPOP) could inhibit cell migration and invasion by downregulation of miR-543 in GC cells [78].
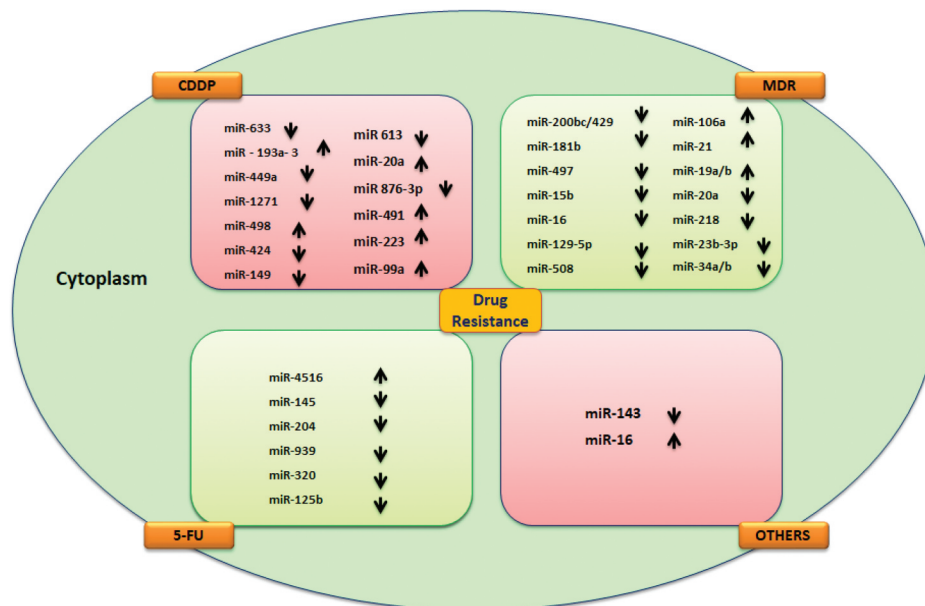
Figure 1. miRNAs associated with chemoresistance in gastric cancer. Drug resistance related to the red and green boxes represents miRNA with expression level,5-FU(5-fluorouracil) MDR (multi-drug resistance), CDDP(cisplatin), and Others.

Qiu et al. found that miR-26a and miR-148a were down-regulated in GC tissues and overexpression of miR-26 inhibit the proliferation, migration, invasion, in GC cell line [79]. Interestingly, miR-610 inhibits the migration and invasion of GC cells by suppressing the expression of vasodilator-stimulated phosphoprotein (VASP) [80]. Similarly, miR-181a directly inhibits caprin-1 and promotes proliferation, apoptosis, migration, and invasion in GC [81].

7. Histological behaviors of miRNAs in GC

On the basis of gene expression, GC cell lines and patients tissue can be classified into three broad categories, intestinal, diffuse and undifferentiated, which overlain with the histological Lauren's classification [82]. Jiang et al. found that miR-421 was overexpressed in GC tissues but had no significant association with the histological behaviors [83]. The weighted gene correlation network analysis (WGCNA) showed that miR 99a, 100, let-7c and 125b associated with the diffuse histological subtype. Beside miR181 family and 21 miR were associated with tumoral phenotype [84]. Recently, Pereira et al. observed that seven miRNAs were differentially expressed in both GC and adjacent GC tissue among them, hsa-miR-200a-3p and hsa-miR-873-5p have diagnostic value for detection of early and advanced disease.

Further, hsa-miR-196a-5p was differentially expressed between adjacent to cancer and GC tissues [85]. The bioinformatics analyses revealed that miR-124 and miR-29b is involved in the tumor stage and serve as a potential biomarker in histological classification of GC [11]. Also, miR-383 levels were down-regulated in intestinal-type GC as compared with non-tumor tissues; this phenomenon was maybe the

promising factor to discriminate intestinal GC patients from healthy controls [86].

8. miRNAs associated with GC stages

The TNM staging is an anatomically based system that primarily used in solid tumor staging to describe the extent and to spread of cancer in a patient. Serum concentrations of miR-21, miR-146a, and miR-148a were significantly associated with pN stage, but not in pT stage. This result suggests that miR may be potential candidates to predict the presence of Lymph Node metastasis in GC [87]. Overexpression of miR-29, miR-196a/196b and miR-630 were found to be associated with GC invasion and metastasis and TNM staging system [88–90]. Wu et al. found that miR-21 Level in serum and peripheral blood mononuclear cells (PBMCs) was significantly associated with early (stage I) and late GC (stage IV) [91]. Recently it was identified that the overexpression of hsa-miR-15b, hsa-miR-18a, hsa-miR-19a, hsa-miR-20a, hsa-miR-22, hsa-let-7i, hsa-miR-93, hsa-miR-106b hsa-miR-196a, hsa-miR-196b, hsa-miR-221, hsa-miR-503, and hsa-miR-545 were significantly associated with GC stages I, II and III compared with normal controls [92].

9. miRNAs and recurrence of GC

GC is clinically heterogeneous and recurrence is the major hindrance to achieve better outcomes. The Cancer Genome Atlas (TCGA) genome-wide data Identified that 312 differentially expressed miR were differentially expressed in 446 GC tissues and signature to predict recurrence in patients with GC [93]. Yan et al.

demonstrated that the up-regulation of hsa-miR-335 has the potential responsible for the recurrence risk and relates to the prognosis of GC patients [94]. Imaoka et al. showed that downregulation of serum miR-203 significantly involved in the prediction of metastases, early recurrence, and poor prognosis in human GC [95].

Similarly down-regulated serum miR206 level might not only serve as a diagnostic biomarker but also predict cancer recurrence for GC [96]. A frozen and formalin-fixed paraffin-embedded tissue microarray-based study showed that the combination of hsa-miR-375 and hsa-miR-142-5p may act as a positive indicator for recurrence and poor survival of GC [97]. Xue et al. found over-expression of miR-328 in early GC tissues and recurrence-free rate was significantly longer in those with relatively high expression of miR-328. This data indicate that miR-328 can function as a predictive biomarker of recurrence [98].

10. Clinical diagnostic of miRNA in GC

Due to the poor diagnosis, lack of specific treatment options and resistance to chemotherapeutic drugs, the detection of biomarkers for GC remains a major challenge. Hence, there is an urgent need to establish a reliable method for early detection and diagnosis of GC stages as well as novel treatments to overcome chemoresistance. Until now, there is no prominent biomarker to diagnose GC and its stages efficiently. Over the past years, researchers are considering circulating miRNAs as dynamic budding biomarkers since they work as a tumor suppressor gene as well as oncogene and involved in cell proliferation, differentiation, chemoresistance and metastasis [99]. As miRNAs can prognosticate response to chemotherapy, they can be used as a promising clinical candidate to target GC. Further, the proficiency of response to chemoresistance implies that the expression pattern of various circulating miRNAs carrying significant differences between patients who are chemoresistance and chemosensitive. Different expression patterns of circulating miRNAs in laboratory specimens might help us to discriminate between responder patients and non-responders to a specific treatment.

In some in vitro studies, demonstrated variations in the expression of different miRNAs between chemotherapy resistance GC cell lines and sensitive control CG cell lines. For instance, upregulation of miR-19a and miRNA-19b was observed in a vincristine (VCR) and doxorubicin (DOX) resistant GC cell lines [100]. Significantly upregulated miRNA-21 and miRNA-106a was found in cisplatin-resistant GC cell lines as compared to controls [101,102]. Another study showed that the level of miRNA-195 and miR-378 were upregulated in GC cell lines which are resistant to 5-azacytidine [103].

Downregulation of miRNAs namely miR-15b and miRNA-16 was found in a VCR resistant GC [104]. Moreover, downregulation of miR-508-5p was found in GC cell lines which are resistant toward DOX and VCR [105]. Downregulation of miR-181b and miR-497 was found in VCR resistant GC cell [106,107]. Further, downregulation of miR-567 in GC tissue as compared to healthy tissues and enhanced chemotherapeutic sensitization to 5-FU and oxaliplatin [108].]. A meta-analysis conducted using the expression patterns of 35 circulating miRNAs in GC patients versus healthy controls reported that the miR-21 is most consistently upregulated in GC cells [109].

11. Therapeutic potential

Conventional therapies are too toxic or ineffective due to chemoresistance. Further, many targeted therapies alone are inadequately effective and will have to be used in combination with other therapeutic targets. In the recent era, application of diverse miRNAs as a modulator of chemotherapy sensitivity is an appealing approach as a significant therapeutic aide with traditional chemotherapeutics. Artificial manipulation of specific miRNAs of different concentrations can also help to accelerate sensitivity or decrease resistance toward various chemotherapy drugs. In addition, alteration of miRNA expression leads to resistance of the different malignant tumors to already established chemotherapy treatment was observed. Some recent findings suggest that circulating miRNA based therapy may be an aggressive and challenging way to fight GC.

On the one hand, miRNA based therapy has the potential to significantly inhibit the oncomiRNA by overexpressing the suppressed miRNA and suppressing oncomiRNA by targeting respective signaling pathways, eventually which may result in the decreased neoplastic progression [110,111]. For instance, some studies revealed that miR-34 suppresses oncomiRNA in a few cancer cells, including liver, breast, lung and Gastric cancer [112–114]. Ji et al. found that restoration of miR-34 was significantly associated with inhibition of GC tumorspheres by facilitating the expression of mutated TP53 gene [115]. Besides, Wang et al. reported that the miR-34 specifically targeting the three prime 3′UTR and inhibits the expression of Yin Yang1 (YY1) which was results in reduced tumor growth and proliferation in SC-M1 and AZ521 GC cells [116]. In addition, miRNAs can significantly influence drug-metabolizing enzymes, drug transporters, nuclear receptors, and transcription factors. The knockdown of miR-21 can substantially promote the anti-proliferative effects and apoptosis by CDDP [102]. Furthermore, time to progress (TPP)

associated chemoresistance miRNA expression profile for gastric cancer patients getting CDDP and FU [117]. Till date it is reported a total of 58 miRNAs linked to the TTP of gastric cancer patients and able to modulate apoptosis in vitro [118]. This study identified miRNA-517, miR-518f, miR-519e, miR- 520a, miR-520d, miR-363 that correlated with chemoresistance which, can be used as an aggressive candidate to predict the responsiveness of GC patients to FU chemotherapy. In addition to this, several studies have identified various miRNA expression profiles during drug induced MDR in GC cell lines, which might be useful to predict the chemotherapy responses in GC cells.

12. MiRNAs modulating GC chemoresistance pathways

Various signaling pathways involved in the GC chemoresistance and expression of miRNA during chemoresistance were summarized in Table 2.

13. PTEN/PI3K/AKT/miRNAs signaling

Several studies demonstrated that the phosphatase and tensin homolog (PTEN)/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) is most frequently mutated pathways in all cancers including GC. Dysregulated expression of various miRNAs are correlated with different cancerous phenotypes, including neoplasm growth, angiogenesis, and metastasis by regulating relative signaling pathways in GC. The modulation of PTEN expression is directly associated with the aberrant expression of the miRNA-221/222 cluster in GC cells [121]. PTEN is also an appealing target for miRNA-21 and miRNA-214 that promote rapid proliferation and invasion of GC cells [122,123]. In addition to this, expression of miRNA-375 directly linked to suppression of PI3K/Akt signaling through direct targeting 3-phosphoinositide dependent kinase-1 (PDK1), an activator of Akt eventually that was resulting in reduced viable cells through induction of the apoptotic pathway [124]. Microarray data has also supported that the miRNA-375 is downregulated in GC. It is also noted that the upregulation of miRNA-28 helps in

Table 2. Summary of Molecular signaling pathways involved in miRNA induced chemoresistance in Gastric cancer.

Pathways Involved	miRNA	Regulation	Derived cell line	Resistant to	References
	miR-23a	UP	MGC803/BGC823	PTX	[58]
	miR – 193a-3	UP	MKN45/AGS/KATO III	CDDP	[60]
	miR-200bc/429	Down	SGC7901/VCR/A549/CDDP	VCR, CDDP, VP-16, ADR, 5-Fu	[27]
	miR-181b	Down	-	VCR, CDDP, 5-Fu, VP-16, ADR, MMC	[106]
	miR-497	Down	SGC7901/VCR/A549/CDDP	VCR, CDDP, VP-16, ADR, 5-Fu	[107]
	miR-503	Down	SGC7901	VCR, CDDP	[28]
Apoptosis	miR-143	Down		CDDP, 5-Fu	[39]
	miR-449a	Down	SGC7901	CDDP	[30]
	miR-15b	Down	SGC7901	VCR, CDDP, VP-16, ADR, 5-Fu, MMC	[104]
	miR-16	Down	SGC7901	VCR, CDDP, VP-16, ADR, 5-Fu, MMC	[104]
	miR-1271	Down	SGC7901	CDDP	[35]
	miR-129-5p	Down	BGC823/MKN45	VCR, ADR, CDDP, 5-Fu	[119]
	miR-34c-5p	Down	BGC-823, MGC-803, MKN-45, and SGC-7901	PTX	[31]
	miR-633	Down	SGC-7901, BGC-823, MGC-803, NCI-N87 and AGS	CDDP	[50]
	miR-19a/b	UP	BGC823/SGC7901	CDDP, 5-Fu, ADR	[100]
	miR-106a	UP	SGC7901	CDDP, 5-Fu, ADR	[101]
	miR-21	UP	SGC7901	CDDP, PTX, Trastuzumab	[102]
	miR-19a	UP	BGC823/SGC7901	CDDP	[34]
	miR-103/107	Down	SGC7901/ADR	DOX	[36]
PI3K/AKT	miR-145	Down	MKN-1	5-Fu	[39]
	miR-149	Down	SGC7901	CDDP	[44]
	miR-501	Down	SGC7901	Dox	[45]
	miR 876-3p	Down	SGC-7901/MKN-45	CDDP	[47]
	miR 613	Down	MGC-803, HGC-27, HGC-27, SGC-7901	CDDP	[48]
Autophagy	miR-4516	UP	A549	5-Fu	[120]
	miR-23b-3p	Down	ATG12/HMGB2	VCR, CDDP, 5-Fu	[43]
EMT	miR-217	Down	BGC-823/SGC-7901	PTPN14	[26]
	miR-204	Down	AGS, SGC-7901, MKN-45, MGC-803, BGC-823	5-Fu, L-OHP	[33]
	miR-508	Down	SGC7901/VCR	VCR, CDDP, 5-Fu, ADR	[105]
MAPK	miR-16	UP	SGC7901	VP-16, 5-FU	[104]
Raf/MEK/ERK	miR-939	Down	AGS, BGC-823, HGC-27, MGC-803, MNK-45, SGC-7901	5-Fu	[132]
ERK/AKT	miR-320	Down	SGC7901	5-Fu	[49]
FBXW7	miR-223	UP	SGC-7901/BGC-823	CDDP	[57]
Notch pathway	miR-34a/b	Down	Kato III, AGS, N87, MKN45	CDDP, DOX, DTX, GEM	[115]
NfkB/IB	miR-20a	Down	SGC7901	CDDP, Docetaxel	[38]
WNT and P53	miR-125b	Down	BGC823	5-Fu	[42]
Hedgehog/smoothened	miR-218	Down	SGC7901/ADM and SGC7901/L-OHP	ADR, 5- Fu, L-OHP	[41]
AKT/JNK	miR-498	UP	HGC27, AGS, SNU-1, SNU-5, SNU-16 MKN-28, MKN-45 and BGC-823	CDDP	[62]

GC cell proliferation and invasion by downregulating PTEN [125]. Expression of macrophage migration inhibitory factor (MIF) was found to promote GC cell proliferation via the PI3K/Akt signaling [126]. Downregulated miRNA-451 expression was found in GC,restoration of miRNA-451 leads to the downregulation of MIF that results in decreased GC cell proliferation in reaction to irradiation [127].

14. RAS/RAF/MEK/ERK/miRNAs signaling

The rat sarcoma 2 viral oncogene homolog (RAS)/rapidly accelerated fibrosarcoma (RAF)/MAPK/ERK kinase (MEK)/extracellular signal-regulated kinase (ERK) is a central signaling transduction component that contributes in certain cellular functions in normal homeostasis. It is also termed as mitogen-activated protein kinases (MAPK) that known for its unique ability to convey signals from cell surface receptors to transcription factors in the nucleus [128]. Overexpression of KRAS protein in GC is associated with the expression of miRNA-181c [129]. The miRNA-29s family significantly influencing the Ras/Raf/MEK/ERK signaling pathway by decreasing the expression of Cdc42 and the level of phosphorylation of its downstream molecule PAK1, thereby resulting in reduced GC cell proliferation [130]. The miRNA-107 as a tumor suppressor and potentially reduced the expression of cyclin-dependent protein kinase 6 (CDK6) that leads to a decline in GC cell proliferation [131]. One recent study demonstrated that the increased expression of miRNA-939 reduces the proliferation, migration, and invasion in GC and contributes to chemosensitivity via inhibiting SLC34A2/Raf/MEK/ERK cascade [132].

15. Slit/Robo/miRNAs signaling

The Roundabout (ROBO) is a transmembrane receptor that binds to SLIT, a secretory glycoprotein ligand that modulate the function of neurons and glia, leukocytes, and endothelial cell migration [133]. Slit-Robo is plays a crucial role in tumor progression by taking part in the cell cycle, cell adhesion, motility, angiogenesis, apoptosis, and invasion [134]. The dysregulation of the Slit-Robo pathway modulates several oncogenic signaling pathways that are coupled with the growth and progression of cancer. The miRNA-218 genes transcribe together with Slit genes, which binds to the Robo1 receptor, thus creating a negative feedback loop that negatively regulates Slit/Robo1 signaling [135]. A recent study showed that the expression of miRNA-218 increases the methylation of SLIT2 or SLIT3 [136].

16. JAK/STAT/miRNAs signaling

The JAK/STAT signaling cascade is one of the principal molecular signaling mechanisms such as cell growth, proliferation, differentiation, cell migration, apoptosis,

inflammation, and survival of immune cells [137]. The JAK/STAT interaction is specifically concerned for a wide array of growth factors and cytokines such as IFNα, IFN-γ and IL-6 mediated signaling [138]. Janus kinase family consists of four members coding as JAK1, JAK2, JAK3, and TYK2. JAK1, JAK2, and TYK2 are ubiquitously expressed cytoplasmic non-receptor. The expression of JAK3 is only restricted to the hematopoietic cells and responsible for hematopoietic differentiation. The miRNA-375 reduced GC cell proliferation and metastasis by targeting the JAK2 gene [139]. The miRNA-135a represses p-STAT3 by targeting JAK2 thus resulting in reduced expression of cyclin D1 and Bcl-xL and suppressed GC metastasis [140]. Further, over-expression of miRNA-18a in GC which negatively regulates the expression of PIAS3, thereby resulting in increased STAT3 signaling [141]. A recent study demonstrated that the miRNA-340 affects GC cell proliferation, cell cycle blocking, and promoting apoptosis through SOCS3/JAK-STAT signaling pathway [142].

17. WNT/beta-Catenin/TCF/miRNAs signaling

The canonically known WNT/beta-catenin signaling cascade is activated by the binding of WNT glycoproteins as a ligand to membrane-bound Frizzled receptors and co-receptor namely low-density lipoprotein receptor-related protein (LRP5/6) eventually phosphorylate Disheveled (Dsh) by requiting it in the membrane. Dsh inhibits the phosphorylation of b-catenin by disrupting the Wnt-Fz-LRP5/6 complex consisting of the adenomatous polyposis coli, Axin and glycogen synthase kinase-3b proteins which resulting in the stabilization of b-catenin. Further, this accumulated unphosphorylated beta-catenin travels to the nucleus and forms complex with transcription factors of the T-cell factor/lymphoid-enhancer factor (TCF/LEF). This complex activates WNT target for transcription specific genes i.e. c-Myc, cyclin D1, gastrin and ITF-2 [143,144]. The miRNA-27a inhibits the expression of Sp-1 repressor mRNA (ZBTB10) that contribute to GC cell survival, cell growth and angiogenesis [145]. Increased expression of miRNA-10b caused a decrease in MAPRE1 expression which may serve as a direct and appealing target of GC [146]. Besides this, another study showed that MAPRE1 might also function as an oncogene through activating the beta-catenin/TCF signaling to promote cell growth and inhibit cell death via apoptosis in GC [147]. The miR-27 by modulating the WNT signal transduction pathway induce GC growth and metastasis [148]. Further, miR-144, the-miR-148a, and miR-193b, were significantly downregulated in GC patients through WNT/beta-catenin pathway [149,150].

18. Concluding remarks

Standard tumor markers, such as serum levels of CA 72–4, carcinoembryonic antigen (CEA), CA 19–9, and

alpha-fetoprotein (AFP) are commonly used for diagnosing advanced disease but not in the early stage of GC patients due to its poor sensitivity and specificity. miRNA regulates expression of proteins that modulate chemosensitivity and chemoresistance to a cancer drug. Many studies found that alterations in miRNA expression differ for specific phases and types of GC, suggesting miRNAs may play a functional as well as novel and potential targets for the treatment of GC.

The expression of specific miRNA might moderately improve chemosensitivity and potentially enhance the antitumor properties of certain drugs. Another rising strategy that can modify gene specific limitations is the machinery of genome editing by clustered regulatory interspaced short palindromic repeats-associated endonuclease 9 (CRISPR-Cas9), which is a quick and efficient ways to down or upregulate the genes, including miRNAs. At present, the comprehensive understanding of the emerging role of miRNA in chemoresistance is unknown. However, further research still needed for the investigation of the sensitivity and specificity of miRNAs that can control GC progression. Overcoming the above challenges will help us to use the miRNAs as biomarkers for the precise management of GC. Many researchers agree that, in near future miRNA will be used as the most important diagnostic and prognostic tool.

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