

WJG 20<sup>th</sup> Anniversary Special Issues (8): Gastric cancer**MicroRNAs: Promising chemoresistance biomarkers in gastric cancer with diagnostic and therapeutic potential**

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Received: March 3, 2014 Revised: April 29, 2014

Accepted: May 26, 2014

Published online: October 14, 2014

**Abstract**

Gastric cancer (GC) is the fourth most common cancer worldwide and ranks second in global cancer mortality statistics. Perioperative chemotherapy plays an important role in the management and treatment of advanced stage disease. However, response to chemotherapy varies widely, with some patients presenting no or only minor response to treatment. Hence, chemotherapy resistance is a major clinical problem that impacts on outcome. Unfortunately, to date there are no reliable biomarkers available that predict response to chemotherapy before the start of the treatment, or that allow modification of chemotherapy resistance. MicroRNAs (miRNAs) could provide an answer to this problem. miRNAs are involved in the initiation and progression of a variety of cancer types, and there is evidence that miRNAs impact on resistance towards chemotherapeutic drugs as well. This current review aims to provide an overview about the potential clinical applicability of

miRNAs as biomarkers for chemoresistance in GC. The authors focus in this context on the potential of miRNAs to predict sensitivity towards different chemotherapeutics, and on the potential of miRNAs to modulate sensitivity and resistance towards chemotherapy in GC.

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**Key words:** MicroRNAs; Biomarker; Chemoresistance; Gastric cancer; Diagnostic; Therapeutic

**Core tip:** MicroRNAs (miRNAs) are a relatively new class of gene expression regulators, being involved in cancer initiation and progression. There is evidence that miRNAs impact on resistance towards various chemotherapeutics and are accessible and detectable in different tissue types, including blood samples, with great stability. Taken together, miRNAs seem to have great potential as new biomarkers for diagnostic and therapeutic approaches. This current review aims to provide an overview about the potential clinical applicability of miRNAs as biomarkers for chemoresistance in gastric cancer (GC), focusing on prediction and modulation of sensitivity and resistance towards chemotherapeutic drugs in GC.

Matuszcak C, Haier J, Hummel R, Lindner K. MicroRNAs: Promising chemoresistance biomarkers in gastric cancer with diagnostic and therapeutic potential. *World J Gastroenterol* 2014; 20(38): 13658-13666 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i38/13658.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i38.13658>

**INTRODUCTION**

Gastric cancer (GC) is the fourth most common cancer worldwide and ranks second in global cancer mortality

statistics<sup>[1]</sup>. The prognosis of GC is poor with an overall 5-year survival rate of less than 35%<sup>[2,3]</sup>, mostly caused by locally advanced disease at the date of initial diagnosis, reduced response to neoadjuvant or adjuvant therapy or tumor recurrence after surgical resection. Surgery is the preferred primary treatment option for the early stage of GC. Unfortunately, over 60% of the patients present advanced stage disease at the time point of diagnosis. In these cases, perioperative chemotherapy is widely applied based on the data of the MAGIC<sup>[4]</sup> and the ACCORD trials<sup>[5]</sup>, including for example platinum- and fluoropyrimidine-based regimen or three-drug protocols with additional application of taxanes or anthracyclines<sup>[4,6,7]</sup>. These therapies are recommended nowadays even for patients with uT2 tumors<sup>[8,9]</sup>. However, response of the individual patient to this perioperative treatment varies widely, and some tumors are resistant to chemotherapeutic treatment completely. Hence, one main obstacle in the success of perioperative chemotherapy is the development of multi-drug resistance (MDR) in GC<sup>[10]</sup>. Based on the current literature, there are four major mechanisms that contribute to drug resistance in cancer cells: (1) decreased uptake of water soluble drugs<sup>[10]</sup>; (2) changes in intracellular pathways that affect the potential of cytotoxic drugs to kill cells, including alterations in the cell cycle, DNA repair, apoptosis pathways, metabolism/elimination of drugs, or others<sup>[10-12]</sup>; (3) increased energy-dependent efflux of hydrophobic drugs mediated *via* overexpression of a family of energy-dependent transporters (known as ATP-binding cassette transporters) such as P-glycoprotein 1 (P-gp, ABCB1) or breast cancer resistance protein (ABCG2) amongst others<sup>[10]</sup>; and (4) intracellular detoxifiers such as antioxidants (*e.g.*, glutathione)<sup>[13,14]</sup>. Unfortunately, from a clinical point of view, there are so far no reliable biomarkers available that allow a prediction of response to chemotherapy in the individual patient before the start of treatment<sup>[15]</sup>. This leads to the problem that a number of patients undergo futile treatment with potential severe side-effects but without any benefit. If response to chemotherapy can be predicted before treatment, therapy could be better tailored *via* identification of patients that in fact profit from chemotherapy.

In this context, microRNAs (miRNAs) could provide a new approach for better clinical decision making. miRNAs are a relatively novel class of regulatory molecules that control translation and stability of messenger RNA (mRNAs) on a post-transcriptional level *via* interaction with the 3'-untranslated region (UTRs) of target mRNAs, that finally leads to destabilization and/or inhibition of their translation<sup>[16]</sup>. So far, over 2500 human miRNAs have been identified according to the latest release (June 2013) of miRBase database<sup>[17]</sup>, and each single miRNA can potentially target up to hundreds of mRNAs<sup>[18]</sup>. miRNAs are involved in the regulation of almost all physiological processes such as cell development, differentiation, proliferation and apoptosis<sup>[19,20]</sup>. But more importantly, miRNAs have been found to impact on pathogenesis of a variety of human cancers. In this con-

text, miRNAs can be roughly categorized into miRNAs that promote tumor development and growth (so-called oncomiRs), and miRNAs that inhibit tumor progression (so-called tumor-suppressor-miRs)<sup>[21,22]</sup>. Regarding GC, several (*in vitro* and *in vivo*) studies demonstrated according to the findings in other cancer types that tumors or GC cell lines present aberrant miRNA expression pattern compared to controls (normal gastric cell lines or samples from healthy patients)<sup>[23-31]</sup>. In conclusion, this data highly suggests that miRNAs may have an enormous potential as diagnostic<sup>[32]</sup>, prognostic<sup>[33-35]</sup>, or even therapeutic biomarkers<sup>[36,37]</sup>.

This current review article now aims to summarize the evidence available so far about the impact of miRNAs on MDR in GC. We aim to specifically highlight from a clinical point of view, that miRNAs might help to predict tumor response to conventional chemotherapy, thereby providing a new approach as diagnostic biomarkers in GC. Moreover, we intend to show that miRNAs might further provide an enormous potential as therapeutic tools in the battle against GC by modulating and/or reversing MDR.

## GENERAL CONSIDERATIONS ABOUT MIRNAS AS BIOMARKERS FOR CHEMORESISTANCE IN GC

### *MiRNAs: Perfect candidates for biomarkers in clinical settings?*

The National Institutes of Health Biomarkers Definition Working Group defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”<sup>[38]</sup>.

This definition of “a characteristic that is objectively measured and evaluated” implicates that molecular biomarkers which might be useful for prediction of the success of chemotherapy in cancer patients should (1) be easily detectable and assessable in clinical patient samples; and (2) be stably expressed and refractory to degradation in these samples in order to allow proper analysis on clinical samples. Only if these characteristics are present, miRNAs can further be assessed regarding their potential as biomarkers for response prediction.

And in fact, regarding the aspect of easily accessible clinical samples, there is a large body of evidence that shows that miRNAs are indeed detectable in a number of different sample types. For example, miRNAs can be found and analyzed in fresh frozen samples such as tumor biopsies or resection specimens, or in paraffin-embedded tissues<sup>[39]</sup>. Even more interesting from a clinical point of view, miRNAs can be detected as so-called “circulating miRNAs” in a broad variety of human body fluids including urine<sup>[23]</sup>, saliva<sup>[39]</sup>, amniotic fluid<sup>[39]</sup> and pleura fluid<sup>[40]</sup> in healthy volunteers and cancer patients<sup>[25,40-43]</sup>. These circulating miRNAs are considered believed to originate either from immunocytes<sup>[44]</sup>, as byproducts of

dead/dying cells<sup>[44-46]</sup>, or to be secreted actively from tumor cells *via* microvesicles such as exosomes<sup>[44-47]</sup>.

Regarding the stability of miRNA expression in clinical samples, Lu *et al.*<sup>[48]</sup> reported that miRNAs are quite stable in different tissue samples (paraffin-embedded sections, rapid frozen samples) and present unique expression levels in different tissue types (salvia, blood, urine). Moreover, circulating miRNAs have been shown to be highly stable in the peripheral circulation caused for example by binding to RNA-binding proteins<sup>[18,49-51]</sup> or by their excretion in microvesicles<sup>[51-54]</sup>. In addition, Fang *et al.*<sup>[41]</sup> reported that miRNAs present tissue-specific expression patterns with a reproducible and consistent expression. Finally, studies demonstrated that circulating miRNAs are fairly resistant to different pH solutions or repeated freeze-thawing cycles, and they are stable for 24 h at room temperature<sup>[55,56]</sup>.

Taken together, miRNA expression patterns can successfully be assessed and analyzed in a variety of different samples, including biopsy or resection specimen, or blood samples, what supports the hypothesis that miRNAs could be used as clinically relevant diagnostic or therapeutic molecular biomarkers.

#### **MiRNAs: Do these molecules impact on MDR in general?**

Another aspect of using miRNAs as potential biomarkers for chemoresistance in GC includes their possible impact on MDR in general. Only if there are data available which support that miRNAs modulate drug resistance in general, these molecules might be useful for evaluation of response prediction in GC patients.

And in fact, miRNAs have been proposed to play an important role in the development of MDR in cancer progression<sup>[55-58]</sup>. Despite the fact that this field of research is still in its infancy, it has been demonstrated that miRNAs are highly related to cancer progression (including growth apoptosis, invasion and metastasis) and are responsible for cancer-related inflammation, anticancer drug resistance and regulation of cancer stem cells<sup>[59]</sup>. Most interestingly, a number of miRNAs (such as members of the let-7 family, miR-16, miR-21 or miR-451 amongst others) have been confirmed to impact on more than one anticancer drug and/or to play a role in chemotherapy resistance in more than just one tumor type<sup>[57,60-62]</sup>. In addition, several anti-cancer-drugs target the same cancer-related genes that are targeted and regulated by miRNAs, implicating a link between chemotherapy induced cancer cell death and a modulation of chemotherapy resistance *via* miRNAs<sup>[63-65]</sup>. However, it has to be noted in this respect that the regulation of known cancer-related genes by miRNAs is much more frequently reported simply because these genes are well studied, and not all miRNAs show similar sensitivity phenotypes in different cancer types. Finally, a number of transcripts from drug resistance-related genes may be targeted by more than one miRNA<sup>[66]</sup>.

Taken together, the evidence available so far on miRNA analysis in different sample types, their stability

in various tissues, and their involvement in chemotherapy resistance in general highly supports the hypothesis that miRNAs might be perfect candidates for biomarkers for chemoresistance in GC in clinical settings.

#### **Limitations about the clinical use of miRNAs as biomarkers**

As miRNA research is so far still mostly limited to *in vitro* experiments, its clinical applicability at this stage is somewhat limited, and there are a number of hurdles that need to be overcome before these molecules can be used in standard clinical settings.

With regards to sample acquisition and miRNA extraction for examples from blood samples, it has been demonstrated that several aspects and factors impact on results of miRNA analyses. These include the appropriate selection of samples (*e.g.*, plasma or serum), collection tubes (EDTA, citrate, heparin), extraction methods (phenol/chloroform, silica: distinct differences in required fluid volume, yield, procedural contaminants *etc.*), quality and quantity control, fasting or blood draw timing, all potentially. In addition, there are a number of different miRNA profiling methods including qRT-PCR, microarrays, sequence specific hybridization in solution followed by miRNA molecule counting based on reporter probes, and direct sequencing available, all of which with more or less relevant advantages and disadvantages regarding sensitivity and specificity, absolute quantification/accuracy and flexibility and throughput<sup>[67]</sup>. In general, it can be postulated, that there is a lack of standardized of experimental techniques at this stage, and this impacts clearly on the possibility to compare data of different studies.

With regards to miRNAs as therapeutic tools, *in vivo* data on animal experiments are limited, and there are to our best knowledge so far only two clinical studies on a potential use of miRNAs as therapeutic tools in human beings available or on its way. Both studies do not refer to GC patients. In a phase 2a clinical trial, Janssen *et al.*<sup>[68]</sup> evaluated the safety and efficacy of Miravirsen® (a locked nucleic acid-modified DNA phosphorothioate antisense oligonucleotide that sequesters mature miR-122 in a highly stable heteroduplex, thereby inhibiting its function) in 36 patients with chronic HCV genotype 1 infection. The authors could demonstrate prolonged dose-dependent reductions in HCV RNA levels without evidence of viral resistance and without dose-limiting adverse events and no escape mutations in the miR-122 binding sites of the HCV genome<sup>[68]</sup>. It is worth to mention that in two phase I safety studies in humans with Miravirsen® showed that Miravirsen® was well tolerated with no dose-limiting toxicities<sup>[69,70]</sup>.

The second clinical trial (phase I trial), which is currently recruiting healthy patients as a control group, uses MRX34 (a liposome-formulated mimic of the tumor suppressor miR-34) in patients with inoperable primary liver cancer or metastatic cancer with liver involvement<sup>[71]</sup>. In this trial, the safety, pharmacokinetics and pharmacodynamics MRX34 is being evaluated in healthy patients<sup>[72]</sup>.

**Table 1** MicroRNAs as potential diagnostic biomarkers for chemoresistance in gastric cancer

miRNAs	Regulation	Drug resistance cell lines	Target	Ref.
miR-15b	Down ↓	Vincristine	PTEN	[62]
miR-16	Down ↓	Vincristine	PTEN	[62]
miR-19a/b	Up ↑	Doxorubicin, vincristine	PTEN	[77]
miR-21	Up ↑	Cisplatin	PTEN	[78]
miR-106a	Up ↑	Cisplatin	PTEN	[79]
miR-181b	Down ↓	Cisplatin, vincristine	BCL-2	[82]
miR-497	Down ↓	Cisplatin, vincristine	BCL-2	[83]
miR-200b/c	Down ↓	Cisplatin, vincristine	BCL-2, XIAP	[83]
miR-508-5p	Down ↓	Vincristine, doxorubicin	ABC1, ZNRD1	[81]

The table presents an overview about miRNAs that present different expression pattern between chemotherapy resistant gastric cancer cell lines and controls, including downstream targets and affected chemotherapeutic agents. PTEN: Phosphatase and Tensin homolog; BCL-2: B-cell lymphoma 2; XIAP: X-linked inhibitor of apoptosis protein; ABC1: ATP-binding cassette sub-family B member 1; ZNRD1: DNA-directed RNA polymerase I subunit RPA12; miRNA: MicroRNA.

Taken together, there are many hurdles that need to be overcome before miRNAs can be safely applied as clinical biomarkers or therapeutic tools. Standardization of technical approaches, confirmation of *in vitro* results in animal experiments and finally safety assessment and treatment trials in humans have to show whether these molecules find their way into the daily clinic. However, first results are promising indeed.

## MIRNAs AND MDR IN GC

There are numbers of potential applications for miRNAs as clinically relevant biomarkers. In the context of this review, we focus on two distinct aspects: miRNAs as diagnostic biomarkers, and miRNAs as therapeutic biomarkers.

MiRNAs as diagnostic biomarkers have to meet various requirements, some of which have been discussed in detail in the section above. However, the main requirement of a diagnostic biomarker in cancer is to distinguish between different “subgroups” of patients. For example, patients with cancer should reliably be distinguishable from patients with precancerous conditions or from non-cancer controls<sup>[73-76]</sup>. In this context, a “simple comparison” of miRNA expression pattern between different “subgroups” of patients is needed in order to allocate patients into the respective “subgroups”, and at this stage, there is no need for further information about the exact impact of the respective miRNAs on tumor growth, metastasis, *etc.*

In contrast to this “simple analytic” approach, the use of miRNAs as therapeutic biomarkers mandates different key features: these miRNAs might not be differentially expressed between different subgroups of patients (such as responders and non-responders to chemotherapy). However, manipulation of the levels of these miRNAs should lead to changes in the cellular response of tumors

to anticancer treatment, increasing thereby for example drug resistance. This means that for therapeutic biomarkers, there is a need for further knowledge about the exact mechanisms by which the respective miRNAs finally affect cancer cell behavior. The objective in the establishment of a therapeutic biomarker is to provide a more individualized therapy approach for every tumor type in the future<sup>[73-75]</sup>.

## MiRNAs as promising biomarkers for chemoresistance in GC with diagnostic potential

The potential to predict response to chemotherapy treatment is a promising clinical application of miRNAs. Successful prediction of treatment response would allow a more tailored, individual therapy planning, as patients who do not respond to this treatment modality would not have to undergo futile treatment with potential severe side-effects. However, response prediction of chemoresistance implies that miRNAs exhibit significant and reproducible differences in expression between patients that respond well to chemotherapy compared to patients that show no or minimal response to this treatment option. With other words, miRNA expression pattern should differ between chemotherapy resistant GC tumors and sensitive tumors.

And in fact, some first authors reported results from *in vitro* experiments that showed differing expression pattern of several miRNAs in chemotherapy resistant GC cell lines when compared to sensitive controls (Table 1), with some miRNAs being upregulated in resistant cancer cells, and others being downregulated. For example, Wang *et al.*<sup>[77]</sup> demonstrated an upregulation of miR-19a/b in a vincristine resistant GC cell line (SCG7901/VCR) and a doxorubicin resistant GC cell line (SGC7901/ADR). In addition, Yang *et al.*<sup>[78]</sup> reported that miR-21 was upregulated in cisplatin resistant GC cells (SCG7901/DDP) *vs* controls. Furthermore, miR-106a was shown to be upregulated in a cisplatin resistant GC cell line (SCG7901/DDP)<sup>[79]</sup>. Finally, miR-195 and miR-378 were found to be upregulated in 5-azacytidine resistant GC cell lines (MGC803, SGC7901 and AGS)<sup>[80]</sup>.

Xia *et al.*<sup>[62]</sup> on the other hand showed that miR-15b and miR-16 both were downregulated in a vincristine resistant GC cell line (SGC7901), and Shang *et al.*<sup>[81]</sup> showed that miR-508-5p was downregulated in two GC cell lines resistant towards doxorubicin (SGC7901/ADR) and vincristine (SGC7901/VCR). Furthermore, Zhu *et al.*<sup>[82]</sup> demonstrated in vincristine resistant GC cell lines miR-181b, miR-200b/c and miR-497 to be downregulated compared to controls<sup>[83]</sup>.

Finally, Wu *et al.*<sup>[84]</sup> analyzed miRNA expression patterns in hydroxycamptothecin (HCPT)-resistant and HCPT-sensitive GC cell lines. miR-224 and miR-338-3p were only expressed in HCPT-resistant cells, and miR-141, miR-200a, miR-200b, miR-372, and miR-373 were only expressed in HCPT-sensitive cells<sup>[84]</sup>.

Even more interesting from a clinical point of view, there is some first evidence that alterations in miRNA

**Table 2** MicroRNAs as potential therapeutic biomarkers for chemoresistance in gastric cancer

miRNAs	Regulation	Drug resistance	Target in GC	Drug treatment	Ref.
miR-21	Up ↑	Up ↑	PTEN	Cisplatin	[78]
miR-27a	Down ↓	Down ↓	Cyclin-D1, p21	Vincristine, 5-fluorouracil, cisplatin, doxorubicin	[87]
miR-106a	Up ↑	Up ↑	PTEN	Cisplatin	[79]
miR-195	Up ↑	Up ↑	CDK6, VEGF	5-azacytidine	[80]
miR-378	Up ↑	Up ↑	CDK6, VEGF	5-azacytidine	[80]
miR-449a	Up ↑	Down ↓	BCL-2, CCDN1	Cisplatin	[88]
miR-508-5p	Up ↑	Down ↓	ABCBI, ZNRD1	Vincristine, doxorubicin	[81]

The table presents an overview about miRNAs that impact on chemotherapy resistance in gastric cancer cell lines, including downstream targets and affected chemotherapeutic agents. PTEN: Phosphatase and Tensin homolog; CDK6: Cyclin-dependent kinase 6; VEGF: Vascular endothelial growth factor; BCL-2: B-cell lymphoma 2; CCDN1: Cyclin-D1 gene; ABCBI: ATP-binding cassette sub-family B member 1; ZNRD1: DNA-directed RNA polymerase I subunit RPA12; MiRNA: MicroRNA.

expression pattern might be able to discriminate between responders and non-responders in clinical patient samples (*in vivo*). Kim *et al*<sup>[85]</sup> for example presented data based on biopsy samples from 90 GC patients which were collected prior to chemotherapy. The authors identified a signature of several miRNAs (namely miR-363, miR-518f, miR-519e, miR-520a, and miR-520d) that was correlated to resistance to cisplatin and 5-fluorouracil therapy<sup>[85]</sup>. With regards to blood based circulating miRNAs, the current literature draws a promising picture: Zhu *et al*<sup>[86]</sup> showed in a recent review including 22 studies with a sample size ranging from 37 to 164, that a total of 35 circulating miRNAs were differentially expressed between GC patients and healthy controls. Most interestingly, 6 of these miRNAs (miR-21<sup>[78]</sup>, -27a<sup>[87]</sup>, -106a<sup>[79]</sup>, -195<sup>[80]</sup>, -200c<sup>[83]</sup> and -378<sup>[80]</sup>) were shown to be deregulated in chemotherapy resistant GC cell lines as demonstrated in the *in vitro* experiments in the paragraph above, and to be potentially involved in MDR.

### **MiRNAs as promising biomarkers for chemoresistance in GC with therapeutic potential**

The application of miRNAs as modifiers of chemotherapy sensitivity is an even more interesting approach for a potential clinical use of these molecules, especially as additive treatment with conventional chemotherapeutics. This implicates that artificial manipulation of miRNA levels lead to increased sensitivity or reduced resistance towards various chemotherapeutic drugs. And again, there is growing evidence that modulation of miRNA expression in fact affects resistance of various tumors to chemotherapeutic treatment. However, as this field of research is still very young, results on GC are limited and refer so far only to *in vitro* experiments. *In vivo* studies on human patients with GC are not available yet.

Similarly to the data presented in the section about miRNAs with diagnostic potential, some miRNAs impact on sensitivity towards chemotherapy if their levels were artificially upregulated, others if their levels were downregulated. For example, upregulation of miR-21 or miR-106a was demonstrated to increase cisplatin resistance of GC cells<sup>[78]</sup>, and Deng *et al*<sup>[80]</sup> showed that upregulation of miR-195 or miR-378 led to an enhanced 5-azacytidine re-

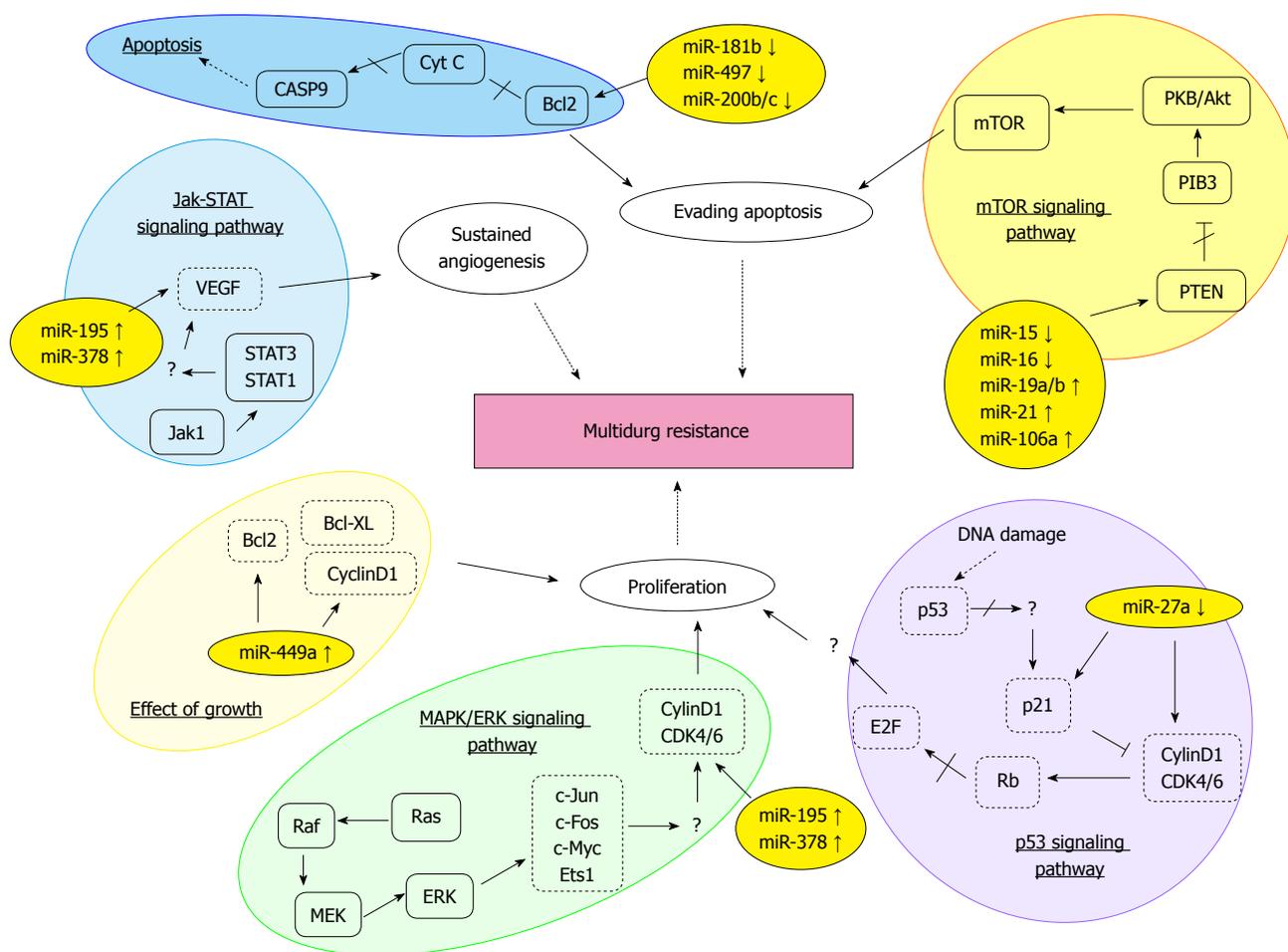
sistance in normal gastric cells. Upregulation of miR-449 or miR-508-5p was demonstrated to positively impact on sensitivity towards cisplatin (miR-449) respectively vincristine or doxorubicin (miR-508-5p)<sup>[81,88]</sup>. Interestingly, in accordance with these findings about the modulation of sensitivity towards chemotherapeutic drugs *via* miRNAs, Bandres *et al*<sup>[89]</sup> reported that upregulation of miR-451 led to an increased sensitivity of cancer cells towards radiotherapy by down-regulating the macrophage migration inhibitory factor (MIF).

Only one research group reported on the effect of miRNA downregulation on chemotherapy resistance: Zhao *et al*<sup>[87]</sup> found that increased doxorubicin sensitivity in GC cells is connected with downregulation of miR-27a.

The authors of the aforementioned studies performed additional experiments in order to elucidate the underlying mechanisms by which the respective miRNAs finally impacted on sensitivity and resistance towards the different chemotherapeutic drugs. Table 2 and Figure 1 present an overview about the results of these investigations, and highlight the downstream targets and pathways that mediate the effects of manipulated miRNA expression in GC cells and their response to anticancer treatment.

## **CONCLUSION**

MiRNAs are an astonishing new class of regulators of global gene expression, and they affect tumor initiation and progression in a large number of malignancies. Moreover, these molecules were shown to impact on sensitivity towards various chemotherapeutic agents in a variety of cancers. Based on the fact that miRNAs play an important role in the development and regulation of MDR, and in addition are accessible and detectable in different tissue types including blood samples with great stability, these molecules seem to have great potential as new biomarkers for diagnostic and therapeutic approaches. In the context of this current review, we presented an overview about the data available so far on this new aspect of miRNAs as biomarkers for chemoresistance in GC. Despite the fact that data on this topic is still somewhat limited, the first reports on miRNAs as po-



**Figure 1 MicroRNAs and their influence on multidrug resistance in gastric cancer.** The figure presents an overview about the targets and pathways that mediate the effects of miRNA manipulation on multidrug resistance in gastric cancer (Data modified from DIANA miRPathv2.0<sup>[90]</sup>). The arrows indicate the up- or down-regulation of miRNA patterns in gastric cancer cells *in vitro*. The dashed boxes indicate nucleus related targets. Interrogation marks represent to date unknown intermediate steps. STAT: Signal transducers and activators of transcription; mTOR: Mammalian target of rapamycin; PKB: Protein kinase B.

tential clinical biomarkers that predict sensitivity towards chemotherapeutic drug are very promising. We found a number of studies that demonstrated various miRNAs to be indeed associated with chemoresistance by presenting different expression patterns between resistant and sensitive tumors, both *in vitro* and *in vivo*. Furthermore, several research groups could provide first evidence that manipulation of the expression of certain miRNAs lead to changes in the sensitivity and resistance of GC towards chemotherapeutics *in vitro*. Taken together, this data draw a very promising picture of miRNAs as potential new biomarkers for chemoresistance in GC with diagnostic and therapeutic potential. This would help to tailor cancer therapy more individually, and to specifically select patients for chemotherapy that would profit from this treatment option. Further research on this highly interesting and clinically most relevant aspect of a potential use of miRNAs is highly warranted.

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ISSN 1007-9327



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