Chapter 6
Current Status of MicroRNA-Based Biomarkers for Gastric Cancer

Prakash C. Sharma and Renu Verma

Abstract Gastric cancer (GC) is a heterogeneous disease and remains one of the leading causes of cancer-related mortalities worldwide. The management of the disease is difficult due to late diagnosis and poor response to available treatment regimes. Currently available gastric cancer biomarkers have serious limitations in their applicability in diagnosis and prognosis of the disease. Therefore, potential biomarkers, particularly with noninvasive assays, are urgently required for the early detection and efficient prediction of therapeutic response and prognosis of gastric cancer. MicroRNAs (miRNAs) are a class of small non-coding RNA sequences that play an important role in modulating key biological processes by regulating the expression of target genes. These molecules are abnormally expressed within the tumor tissues and associated biological fluids including blood, gastric juice, and urine of GC patients. Recent experimental findings have led to the identification of a large number of miRNAs implicated in the occurrence and progression of gastric cancer. miRNAs contribute to gastric carcinogenesis by regulating the expression of different oncogenes and tumor suppressor genes involved in cell proliferation, apoptosis, motility, and invasion. Many miRNAs have been found specifically associated with tumor type, tumor stage, and patient survival. Therefore, miRNAs are now being sincerely investigated as a source of potential biomarkers for the effective management of gastric cancer. Availability of such markers will also assist clinicians in designing precision medicine regimes for personalized treatment of the GC patients and provide potential targets for future drug development. This review summarizes the current knowledge about microRNA markers and their applicability in the diagnosis, prognosis, and prediction of treatment response in gastric cancer.

Keywords Gastric cancer · Biomarkers · MicroRNAs · Diagnosis · Prognosis · Targeted therapy

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6.1 Introduction

Cancer is the second leading cause of death globally accounting for 9.6 million deaths in 2018. Gastric cancer, a heterogeneous disease, is the sixth most common cancer with 1.03 million cases and the third most common cause of 7,83,000 cancer-related deaths. Although the rank of GC incidences has declined from fourth to sixth recently, the number of mortality cases has increased by 5.7%. Approximately, 70% of GC deaths occur in developing countries. Due to its asymptomatic behavior, GC is mostly diagnosed at an advanced stage. The available markers including the most known carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) lack consistency at early stages as compared to advanced stages. Therefore, the development of novel-sensitive biomarkers is imperative for early diagnosis of GC.

MicroRNAs (miRNAs) is a small class of non-coding RNAs of 20–24 base sequence that regulates gene expression at transcriptional and post-transcriptional level and plays a significant role in various physiological and pathological processes (Bartel 2004; Lee et al. 2003). miRNAs have been found to express aberrantly in cancer tissues. Apart from tissues, miRNAs can also be detected in serum, plasma, urine, tears, gastric juice as well. miRNAs traverse into biofluids through exosome particles or microvesicles that protect miRNAs from RNase degradation (Ma et al. 2013). Analysis of plasma and serum remains the most extensively used noninvasive method facilitating screening for miRNA-based diagnostic biomarkers (Link and Kupcinskas 2018). Role of miRNAs has been explored earnestly in oncogenesis, apoptosis, and tumor progression (Ekimler and Sahin 2014; Tian et al. 2014). miRNAs have also shown specific association with tumor type, tumor stage, *Helicobacter pylori* infection and patient survival. The length (~22 bp) and the stability of miRNAs under severe conditions including varying pH and temperatures give an advantage to evaluate them as biomarkers. Various studies have explored the role of miRNA in cancers, and it has been reported that China is the leading researcher in miRNA studies in GC followed by Japan, Taiwan, S. Korea, and Poland. There has been a remarkable increase in the number of miRNA-based studies in GC in this decade (Link and Kupcinskas 2018). In this chapter, we emphasized the role of miRNAs in gene regulation and their potential as diagnostic and prognostic markers in gastric cancer.

6.2 Molecular Classification of GC

Molecular classification of GC has been attempted by different groups, of which the following three recent molecular classifications of GC have been reported here:

1. Singapore Researchers
2. Asian Cancer Research Group (ACRG)
3. The Cancer Genome Atlas (TCGA)

A molecular classification of GC based on gene expression patterns made by researchers in 2013, grouped GC into the following three subtypes (Lei et al. 2013):

(a) Proliferative: This subtype displays high levels of genomic instability, *TP53* mutations, and DNA hypomethylation.
(b) Metabolic: Tumors of this subtype are associated with higher anaerobic glycolysis that makes the cells more sensitive to 5-fluorouracil therapy.
(c) Mesenchymal: Tumors of the mesenchymal subtype exhibit features of cancer stem cells and sensitivity to PIK3CA-AKT-mTOR pathway inhibitors.

Another molecular classification based on molecular alterations, disease progression, and prognosis proposed by the Asian Cancer Research Group (ACRG) in 2015 (Fig. 6.1) has categorized GC into four subtypes (Cristescu et al. 2015):

(a) Mesenchymal like type: It accounts for 15.3% of gastric tumors and includes tumors showing diffuse histology with the worst prognosis. They tend to occur at an advanced stage and an early age. It also showed a loss of CDH1 expression and the highest frequency (63%) of reoccurrence among the four subtypes.
Microsatellite unstable tumors: This subtype represented by intestinal histology exhibits the best prognosis and the lowest frequency (22%) of reoccurrence among all subtypes of ACRG classification and predominantly arises at an early stage of GC.
(b) TP53 active: Tumors of this subtype are characterized by the presence of TP53 mutations, frequent EBV infection, and intermediate prognosis and reoccurrence rates.
(c) TP53 inactive: This subtype is marked by the absence of TP53 mutations, intermediate prognosis, and reoccurrence rates. Recurrent focal amplifications in RTKs had also been observed in the group.

One of the most recent and known classifications has been proposed by the Cancer Genome Atlas Group (TCGA) in 2014 on the basis of copy number variation (CNV), RNA sequencing, miRNA sequencing, exome sequencing, methylation status, and reverse phase protein assay (Cancer Genome Atlas Research Network 2014). This classification accommodates GC into the following four subtypes (Fig. 6.1):

(a) EBV-positive GC: This subtype represents moderately to poorly differentiated adenocarcinoma found in 9% of GC cases and is characterized by the association with Epstein–Barr virus, frequent PIK3CA mutations, and elevated expression of programmed death ligands 1 and 2 (PD-L1 and PD-L2). EBV-positive cancers are more prevalent in males (81% cases), particularly at young age and mainly located in fundus and body region of the stomach.
(b) Microsatellite unstable GC: This subtype characterized by microsatellite instability (MSI) is found in 22% of GC and has been associated with intestinal histology. MSI unstable GC shows CpG island methylation phenotype, including hypermethylation of the MLH1 promoter. Mutational analysis of MSI samples has identified 37 significantly mutated genes including TP53, PIK3A,

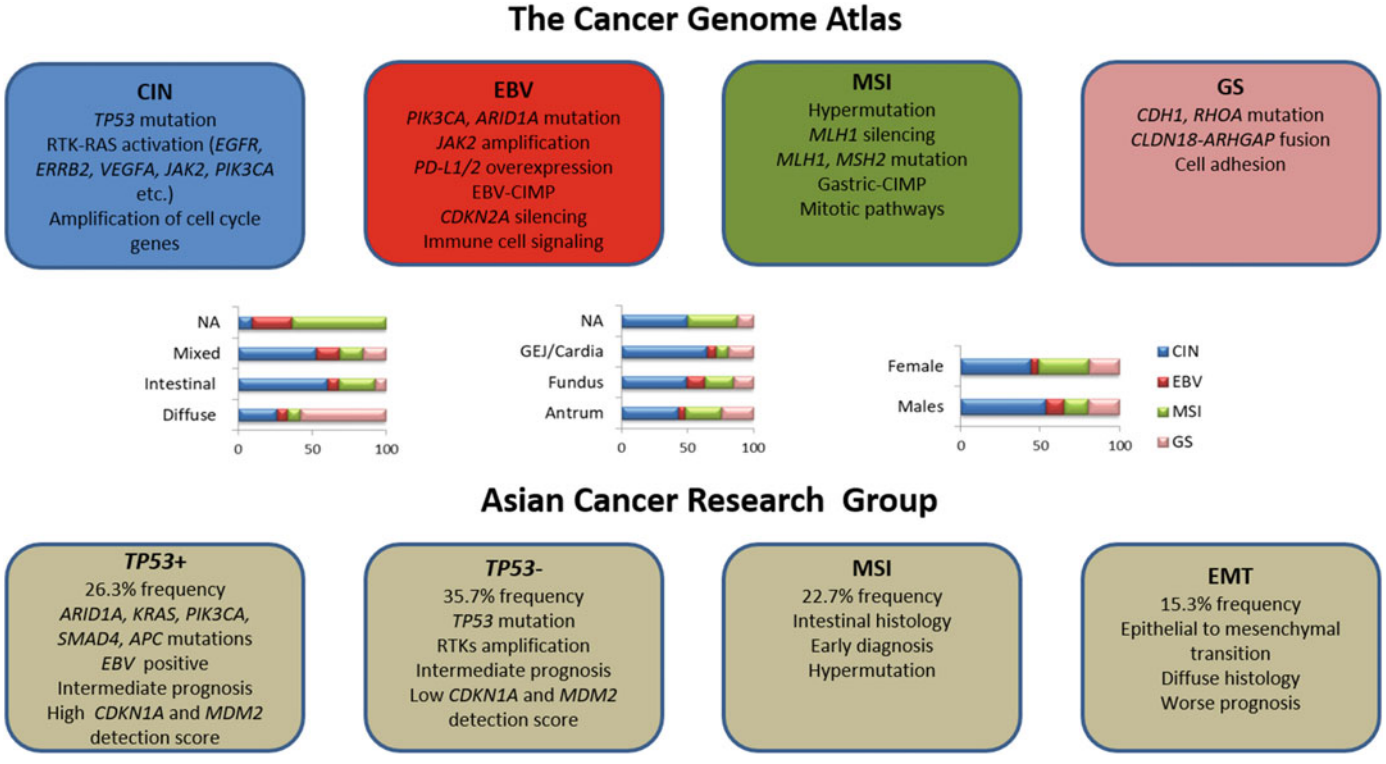

Fig. 6.1 Molecular classification of gastric cancer

KRAS, and ARID1A. Unlike colorectal cancer, BRAF and V600E mutations are not associated with microsatellite unstable GCs. It is more prevalent in females and found mainly in the antrum and pylorus regions. Alteration in MMR genes like *MLH*1 and *MSH2* leads to dysfunctioning of MMR system.

(c) GC with chromosomal instability: This subtype GC account for 50% of incidences that are located predominantly in the gastro-esophageal junction. Association of the intestinal type with copy number gains of chromosomes 8q, 17q, and 20q and diffuse type with gains of chromosomes 12q and 13q has been observed in GC with CIN. The chromosomal instability leads to the loss or gain of function of tumor suppressor and oncogenes. Mutation in TP53 gene, RTKs (receptor tyrosine kinases), and amplification of cell cycle genes are frequent in this subgroup. Amplification in oncogene pathways including MAPK signaling, RAS signaling is also an important feature.

(d) Genomically stable (GS) GC: The subtype is represented by 20% of GC incidences, diffuse histology, early age diagnosis, and comparable occurrence in males and females. Histologically, 25% tumors are located in the antrum, 20% in the gastro-esophageal junction and cardia, and approximately 15% in body and fundus. A recurrent interchromosomal translocation involving CLDN18 and ARHGAP26 has been found implicated in this subtype. The main somatic mutations observed in GS-GCs involve *CDH1*, *ARID1A*, and *RHOA* genes.

6.3 Role of miRNA in Gene Regulation

Aberrant miRNA expression has been found associated with tumorigenesis. Various studies have suggested that miRNAs play a crucial role in gene regulation. A schematic representation of upregulated and downregulated genes involved in GC is given in Fig. 6.2. Convincingly, miRNAs act as critical gene regulators involved in many biological processes.

MicroRNA-targeted tumor suppressor genes show a significantly reduced expression. miRNA-126 which regulates a tumor suppressor gene *PLK2* showed decreased expression in GC tissues. Moreover, miR-126 itself acts as tumor suppressor inhibiting GC cell invasion by targeting *Crk* gene. It also serves as an oncogene by targeting *SOX2* gene in GC (Liu et al. 2014). Inhibition of expression of other tumor suppressor genes, *PDCD4* and *PTEN*, by miRNA-21 results in growth, migration, and invasion of cancer cells in GC (Li et al. 2014).

Similarly, miR-124 suppresses the cell proliferation, migration, and invasion by targeting Rho-associated coiled-coil containing protein kinase 1 (*ROCK1*) (Hu et al. 2014). miR-148a gets inactivated by hypermethylation of the promoter region (Fujita et al. 2010). miRNA-148a suppresses tumor cell invasion by downregulating *ROCK1* (Zheng et al. 2011). Downregulation of miR-125a-5p targets *E2F3* and has been associated with GC metastasis. miR-106a, induced by SP1 and EGR1, downregulates the expression of *IL10* and acts as a regulatory element (Sharma et al. 2009).

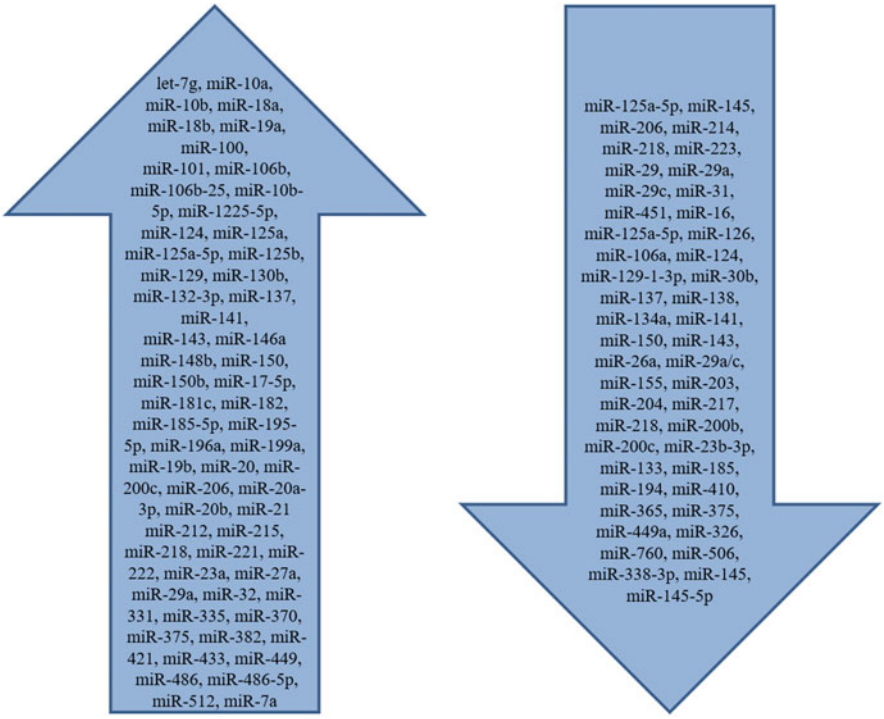

Fig. 6.2 Schematic diagram of differentially expressed miRNAs in gastric cancer

Increased DNA methylation of miR-210 has been linked with GC samples infected with *H. pylori.* Enhanced proliferation resulted from epigenetic silencing of miR-210 in gastric epithelial cells has been observed (Kiga et al. 2014). *H. pylori* infection led to the downregulation of miR-375 by targeting *JAK2* (Janus kinase 2) demonstrating that the JAK2-STAT3 pathway regulated by miR-375 is implied in *H. pylori* induced GC (Miao et al. 2014). miRNAs also play a role in angiogenesis. HIF-1α induced miR-382 targets tumor suppressor gene *PTEN* and acts as an oncogene promoting angiogenesis (Seok et al. 2014).

Expression of miRNA let-7 has been found to reduce the expression of *HRAS*, *KRAS,* and *NRAS* genes. *RAB40C*, a target gene of let-7, has been shown to play a significant role in gastric tumorigenesis (Yang et al. 2011). Enhancer of zeste homolog 2 (*EZH2*) contributes to the epigenetic silencing of target genes and regulates the survival and metastasis of cancer cells. The genomic loss of miR-101 in cancer leads to overexpression of *EZH2*, resulting in cancer progression. Overexpression of *EZH2* has been observed in aggressive solid tumors (Varambally et al. 2008).

6.4 Gastric Cancer Biomarkers

Screening for genomic biomarkers could lead to a better management of GC facilitating early diagnosis, prognosis, and predictable treatment response. Various new approaches have emerged which could be explored for the development of GC biomarkers.

Somatic alterations in short iterations of DNA sequences lead to genomic instability which may result in tumorigenesis. A random clinical trial reported the variation in prognosis of MSI-high and MSS/MSI-low gastro-esophageal cancer when treated with surgery alone and in combination with perioperative chemotherapy. The trial also indicated insignificance of perioperative chemotherapy in MSI-high cases (Smyth et al. 2017). 15–30% of gastric tumors showed MSI, particularly as a result of epigenetic silencing through promoter methylation of *MLH1* (Pinto et al. 2000). Microsatellite-positive tumors with *PIK3CA* mutations have been effectively treated with *PIK3CA* inhibitors as personalized therapy regime in GC patients (Zang et al. 2012). Instability at mononucleotide repeats in *CCDC150, CEP164, CNOT1, KIAA2018, MIS18BP1, RNPC3,* and *TGFBR2* has been reported in 63% of the MSI-positive GC samples (Yoon et al. 2013).

Modifications in the epigenome such as histone modifications and DNA methylation have been related to tumorigenesis in different cancers. Inactivation of tumor suppressor genes by methylation in the promoter region of the genes is a well-known feature observed in GC. Serum-based diagnostic markers (*CDH1, CHFR, P15. P16, RARβ, RUNA3*, etc.) exhibiting defective DNA methylation in GC has been previously presented (Qu et al. 2013). CHFR promoter methylation has also been linked to differentiation and lymph node status of GC (Ding et al. 2018). Loss of *FAT4* expression in methylated GC cell lines was observed by Yoshida and co-workers (Yoshida et al. 2017). Epigenetic profiles could serve as early diagnostic and prognostic biomarker in GC.

Experimental studies have demonstrated the implication of genetic polymorphism in Interleukin-1β in GC (Drici et al. 2016). Single nucleotide polymorphism in *CD44* gene has been suggested prognostic biomarker for early recurrence in GC (Suenaga et al. 2015). *CDH1, CSMD3, LRP1B, PIK3CA, ARID1A, TP53, SYNE1,* and *PKHD1* were among the top mutated genes displaying copy number variations in GC patients (Kuboki et al. 2016). Another study reported copy number variation in *KRAS*, *JAK2*, *CD274,* and *PDCD1LG2* (Hou et al. 2015).

6.5 miRNA Biomarkers

Gastric cancer being asymptomatic in nature is often diagnosed at an advanced stage. Thus, the need for biomarkers to detect GC at early stages is the primary objective of cancer management. Researchers have been exploring the feasibility of utilizing miRNAs as biomarkers considering the expression changes in tumor tissues and

Table 6.1 Important upregulated miRNAs involved in GC with their target genes and function

miRNA	Target gene(s)	Function
miR-92	*FXR*	Invasion, Proliferation
miR-21	*PTEN, TIMP1*	Apoptosis, Invasion, Migration, Proliferation
miR-107	*DICER1*	Invasion, Migration
miR-25	*FBXW7*	Invasion, Migration, Proliferation
miR-106b	*PTEN*	Invasion, Migration
miR-500	*NF-kB*	Apoptosis, Proliferation
miR-124	*ROCK1*	Invasion, Proliferation
miR-146a	*EGFR*	Invasion, Migration
miR-150	*EGR2*	Apoptosis, Proliferation
miR-200c	*CDH, RHO*	Metastasis
miR-210	*STMN1, DIMT1*	Angiogenesis
miR-181a	*PTEN*	Proliferation
miR-181c	*KRAS, NOTCH4*	Proliferation
miR-183	*PTEN*	Migration
miR-449	*MET, SIRT1, CDK6*	Apoptosis, Cell cycle, Proliferation
miR-221	*CDKN1A, CDKN1B, CDKN1C*	Cell cycle
miR-222	*CDKN1A, CDKN1B, CDKN1C*	Cell cycle
miR-421	*BAX, BCL-2*	Oncogenes
miR-362	*NF-kB*	Anti-apoptotic
miR-382	*PTEN*	Angiogenesis
miR-377	*P53, PTEN, TIMP1*	Proliferation
miR-520d-3p	*EPHA2*	Inhibits proliferation and invasion
miR-508	*INPP5J*	Invasion, Migration, Proliferation
miR-942	*SFRP4, GSK3B, TLE1*	Proliferation
miR-1288	*FOXO1*	Proliferation
miR-125a-5p	*ERBB2, E2F3*	Invasion, Metastasis, Migration, Proliferation

biofluids as well indicating their involvement in proliferation, invasion, metastasis, and tumorigenesis (Tables 6.1 and 6.2).

6.5.1 Diagnostic Markers

Various studies based on the expression profile and next-generation sequencing has provided useful evidence to highlight the diagnostic potential of miRNA in GC.

6.5.1.1 Blood-Based Markers

mi-375 showed decreased expression in distal gastric adenocarcinoma tissues and significant downregulation in serum samples in comparison to control samples

Table 6.2 Important downregulated miRNAs involved in GC with their target genes and function

miRNA	Target gene(s)	Function
miR-16	*P53*	Proliferation
miR-125a-5p	*ERBB2, E2F3*	Invasion, Metastasis, Proliferation
miR-126	*PI3KR2, CrK, PLK2*	Invasion, Metastasis, Proliferation
miR-106a	*EGFL7, E2F1*	Invasion, Migration
miR-124	*ROCK1*	Inhibits proliferation
miR-129-1-3p	*BDKRB2, PDCD2*	Inhibits migration
miR-30b	*PAI-1*	Apoptosis
miR-137	*AKT2*	Proliferation
miR-138	*NF-Kb*	Proliferation
miR-134a	*FSCN, MMP14*	Invasion, Migration
miR-141	*ZEB1, ZEB2*	Invasion, Migration
miR-150	*ZEB1*	EMT
miR-143	*TLR2*	Invasion, Migration
miR-26a	*FGF9*	Metastasis, Proliferation
miR-29a/c	*VEGF*	Metastasis, Proliferation
miR-155	*c-myc*	Invasion, Proliferation
miR-203	*E-cadherin*	EMT, Migration
miR-204	*SOX4*	Invasion, Proliferation
miR-217	*EZH2*	Invasion, Metastasis, Proliferation
miR-218	*ROBO1*	Apoptosis, Invasion, Proliferation
miR-200b	*DNMT3A, DNMT3B, SP1*	Proliferation
miR-200c	*ZEB1, ZEB2*	Invasion, Migration
miR-23b-3p	*ATG12, HMGB2*	Chemoresistance
miR-133	*CDC42-PAK*	Invasion, Migration, Proliferation
miR-185	*DNMT1, CDC42*	Metastasis
miR-194	*RBX1*	Migration, Proliferation
miR-410	*MDM2*	Inhibits invasion and migration
miR-365	*Cyclin D1, BCL-2*	Apoptosis
miR-375	*PDK1, JAK2*	Inhibits proliferation
miR-449a	*CDK6*	Apoptosis
miR-326	*FSCN1*	Migration, Proliferation
miR-760	*HIST1H3D*	Migration
miR-506	*YAP-1*	Invasion, Proliferation
miR-338-3p	*SMO*	Apoptosis
miR-145	*ETS1*	Angiogenesis, Invasion, Migration
miR-145-5p	*TLR4, KLF5*	Inhibits proliferation

($p < 0.001$) (Tsujiura et al. 2010). Tsujiura et al. reported increased expression levels of miR-21 ($p = 0.05$), miR-17-5p ($p = 0.006$), miR-106a ($p = 0.008$), and miR-106b ($p < 0.001$) in plasma. Decreased expression of let-7a ($p = 0.002$) was also reported suggesting the role of all these miRNAs as tumor markers for GC diagnosis (Tsujiura et al. 2010). *H. pylori* infection has been linked with miRNA

expression levels. It was proposed that serum miR-106b was significantly overexpressed before and after eradication of *H. pylori* as compared to healthy controls where miR-21 showed significantly high expression after *H. pylori* eradication when compared with healthy controls in GC patients (Shiotani et al. 2013).

The plasma levels of miR-223 ($p < 0.001$) and miR-21 ($p < 0.001$) were found significantly higher in GC patients than in healthy controls while miR-218 was significantly lower ($p < 0.001$). The combined ROC analysis of all the three miRNA revealed AUC value of 0.953 in discriminating GC patients from healthy controls. Also, a correlation between expression levels of miR-223 with *H. pylori* infection was reported (Li et al. 2012).

Expression of three miRNAs has been validated for early detection of GC using qRT-PCR. Here, the level of expression was first checked in a cohort of 30 patients and then validated on a sample size of 60 patients diagnosed with GC. Upregulation of miR-106b, miR-20a, and miR-221 ($p < 0.05$) in plasma suggested their potential role as early-stage biomarker. The area under ROC curves was 0.773 for miR-106b, 0.859 for miR-20a, and 0.796 for miR-221. The three markers might be useful together as a panel of biomarkers for diagnosis (Cai et al. 2013). Liu et al. reported elevated levels of miR-187 ($p = 0.0016$), miR-371-5p ($p < 0.0009$), and miR-378 ($p < 0.0001$) in serum samples of GC patients. The ROC curve area of miR-378 was 0.861 with 87.5% sensitivity and 70.73% specificity. Further, the inclusion of miR-187 and miR-371-5p did not improve the discrimination value significantly (Liu et al. 2012).

Plasma samples of 12 GC patients with distant metastasis observed significantly lower and higher levels of miR-122 and miR-192 with AUC 0.808 and 0.732, respectively (Chen et al. 2014a). Zhu et al. screened 36 patients diagnosed with gastric cardia adenocarcinoma (GNCA) along with 160 cancer-free controls for recording the expression level of miRNA. The study revealed overexpression of miR-16, miR-25, miR-92a, miR-451, and miR-486-5p as a suggestive biomarker in detecting the early stage GC (Zhu et al. 2014).

A microarray experiment was performed on 123 patients and 111 healthy controls to identify deregulated miRNAs in GC. Overexpression along with high sensitivity (86.7%) and specificity (85.5%) of miR-627, miR-629, and miR-652 were observed which show their potential for use as a panel of potential biomarkers (Shin et al. 2015). Overexpression of miRNA-185, miR-20a, miR-210, miR-25, miR-92b ($p < 0.05$), miR-10b-5p, miR-132-3p, miR-185-5p, miR-195-5p, miR-20a-3p, and miR-296-5p has been observed by different group of researchers (Zhou et al. 2015; Huang et al. 2017). Involvement of miR-940 in the initiation and progression of GC through NF-κB and Wnt/β signaling pathway was predicted in plasma and cell lines of GC patients (Liu et al. 2016).

6.5.1.2 Tissue-Based Markers

The expression levels of miR-106a, miR-421, and miR-21 were significantly higher while the level of miR-31 significantly downregulated in GC tissue samples (Xiao

et al. 2009; Chan et al. 2008; Jiang et al. 2010; Zhang et al. 2010). miRNA with dysregulated expression can play a tumor suppressor or an oncogenic role. Overexpressed miR-21 binds to *PDCD4*, a tumor suppressor gene, and inhibits its protein expression. The miR-21 expression has been related to tumor size, depth of invasion, lymph node metastasis, and vascular invasion (Li et al. 2012; Chan et al. 2008; Motoyama et al. 2010). Other miRNAs such as miR-32, miR-182, miR-143, and miR-106a have been found upregulated in GC tissues (Xiao et al. 2009; Li et al. 2011). The expression level of miR-106a is closely related to the size of the tumor, differentiation status, lymph node involved, and distant metastasis (Xiao et al. 2009). miR-31, miR-218, and miR-223 are tissue-based downregulated miRNA biomarkers in GC (Li et al. 2012; Zhang et al. 2010). The sensitivity of miR-421 in GC tissues has been observed to be more than serum carcinoembryogenic antigen which indicates its potential as a diagnostic marker (Jiang et al. 2010).

6.5.1.3 Biofluid-Based Markers

Gastric juice: Although the collection of gastric juice from the patients through gastroscopy or evacuated tubes is invasive but the examination of miRNA in gastric juice could result in better treatment prediction of GC. miRNAs have been observed to withstand low (pH = 1) to high (pH = 13) making them suitable for gastric juice-based studies (Chen et al. 2008). Discrimination of GC from healthy and benign gastric disease with miR-421 and miR-133a in gastric juice has been realized (Shao et al. 2016; Zhang et al. 2012). The miR-21 and miR-106a in gastric juice, when used together, have been observed to detect GC up to 98% (Cui et al. 2013). The low expression levels of miR-129-1-3p and miR-129-2-3p in gastric juice were analyzed in GC patients (Cui et al. 2013).

Urine: Diagnostic value of miR-376c has been observed in GC patients where the level of its expression in urine was found to be increased (Hung et al. 2017). Another study exhibited high expression of miR-21-5p in urine samples of GC patients compared to the healthy controls. The levels of miR-21-5p significantly reduced after surgical resection (Kao et al. 2017).

Exosomes: They are small vesicles enclosed by lipid bilayer membrane in the extracellular environment that are secreted by cells and contain a variety of molecules including miRNAs. Alike miRNA in gastric juice is protected from varying pH; the miRNA is protected in exosomes from ribonuclease degradation (Valadi et al. 2007). Levels of miR-221 in exosomes from peripheral blood were found to be increased by 2.5 fold in GC patients compared to healthy controls. Exosomal miR-106a-5p and miR-19b-3p were found to be elevated in GC patients and exhibited 81% detection ability when combined together (Wang et al. 2017).

6.5.2 Prognostic Markers

Apart from being suitable diagnostic markers, the prospective role of miR-21, miR-106a, and miR-106b as prognostic markers was reported in plasma samples of GC patients. Overexpression of miR-21 has been correlated with vascular invasion ($p = 0.0311$) and could be used as an independent prognostic biomarker in GC. Correlation of tumor size and stage with miR-21 expression has been established (Komatsu et al. 2013; Kim et al. 2013).

miR-20a and miR-17-5p have been found significantly correlated with differentiation, staging, and poor overall survival. A decrease in the expression level of miR-17-5p and miR-20a was observed in response to chemotherapy (Wang et al. 2012). miR-20a solely showed the potential ability to be a prognostic marker. Expression of miR-17-5p as a prognostic marker and in the assessment chemotherapeutic effects on GC has been detected (Komatsu et al. 2013; Wang et al. 2012).

The expression level of miR-196a in serum and tissue of GC patients was found correlated with progression and relapse of GC (Tsai et al. 2012). Another microRNA, miRNA-195-5p, with prognostic value has been observed (Gorur et al. 2013). Low expression of let-7a miRNA in serum and tissue samples of GC was observed and correlated with lymph node metastasis, depth of invasion, staging, tumor size, and progression of GC (Wang et al. 2013). Association of expression of miRNA with GC metastasis has been analyzed. Decreased expression of miR-218 in the serum sample of GC patients and high expression of mi-214 in plasma and serum samples has been associated with GC metastasis (Xin et al. 2014; Zhang et al. 2015). The levels of miR-214 were significantly decreased after surgical resection.

Overexpression of miR-25 is correlated with lymph node metastasis by targeting TOB1 (Li et al. 2015). Correlation between low levels of miR-203 and metastasis was found and an inverse relation between GC development and level of miR-203 was analyzed by Imaoka group (Imaoka et al. 2016). miR-29 and miR-106b are tissue-based miRNAs found associated with poor prognosis with low and high expression levels, respectively. miR-125a-5p and miR-206 are independent prognostic factor showing downregulation in GC patients (Yang et al. 2013; Nishida et al. 2011). A study analyzed seven miRNAs (miR-10b, miR-21, miR-223, miR-338, let-7a, miR-30a-5p, miR-126) significantly related to recurrence-free periods and overall survival of patients (Li et al. 2010). Upregulated miR-125b, miR-199a, and miR-100 have shown association with progression of GC (Ueda et al. 2010).

6.5.3 Therapeutic Markers

The potential prognostic and diagnostic markers undergo clinical trials to improve cancer treatment regimes. Evidence suggests that miRNA therapeutics have been evaluated in both preclinical and clinical settings. Moreover, the probability of

miRNA in drug resistance has been explored. The expression of miR-218 has been demonstrated to increase in vitro cell chemosensitivity to drug cisplatin and decrease tumor growth (Zhang et al. 2014).

Overexpression of miR-362 induced cell proliferation and resistance to cisplatin induced apoptosis in BGC-823 and SGC-7901 GC cells (Xia et al. 2014). miR-129 has been used as a novel therapeutic target in gastrointestinal marker (Fesler et al. 2014). An inverse relation between the expression level of miR-196a/miR-196b and *RDX* protein levels have been observed. Reduced miR-196a/miR-196b levels or increased level of the *RDX* gene have a potential therapeutic role in GC metastasis. Cisplatin resistance of GC cell lines is found to be regulated by miR-503 by targeting *IGF1R* and *BCL2* (Wang et al. 2014). Similarly, miR-1271 targets BCL2, IGF1R, IRS1, and mTOR genes and has shown to regulate cisplatin resistance in GC cell lines (Yang et al. 2014).

miRNAs such as miR-92b and miR-422a have been found associated with relapse following chemotherapy in GC (Omura et al. 2014). Shen et al. described the importance of clinical efficacy of DNA damage inducing chemotherapeutic drug by reducing drug resistance. The study analyzed that doxorubicin downregulates HDAC1 protein expression which is a target gene of miR-520 h (Shen et al. 2014). miR-1207-5p and miR-1266 are significantly decreased in GC tissues and their ectopic expression inhibits tumor growth by suppressing hTERT. These miRNA provides a novel therapeutic approach for GC treatment (Chen et al. 2014b).

6.6 Future Perspectives

miRNA have emerged as crucial translational gene regulators in cancers including gastric cancer. The discovery of noninvasive and specific biomarkers which could provide early detectability and personalized treatment is needed. Although the development of miRNA-related biomarkers is still in the preclinical stages, they hold huge potential as biomarkers facilitating early diagnosis, prognosis, and therapeutics in gastric cancer. Being a heterogeneous disease, GC shows different outcomes in the similar clinical and pathological conditions. Therefore, the novel biomarkers need to be based on genome analysis ensuring prevention and treatment of the disease. Molecular classification in combination with the histological classification of GC could be used as a platform to explore the underlying mutations in GC and to design prognostic and therapeutic regimes. Several reports in contemporary literature have advocated the use of single/combinations of biomarkers in GC that can predict favorable or unfavorable response towards single/multidrug treatment regimes (Duraes et al. 2014). MicroRNAs with multi-functional characteristics, i.e., a single microRNA with diagnostic, prognostic, and therapeutic role are desired for the development of efficient biomarkers (Fig. 6.3). GC-specific miRNA have been associated with tumor formation, proliferation, and metastasis. Future studies with identification and validation of miRNA-based diagnostic, prognostic, and therapeutic biomarker will aid to the better understanding and management of GC.

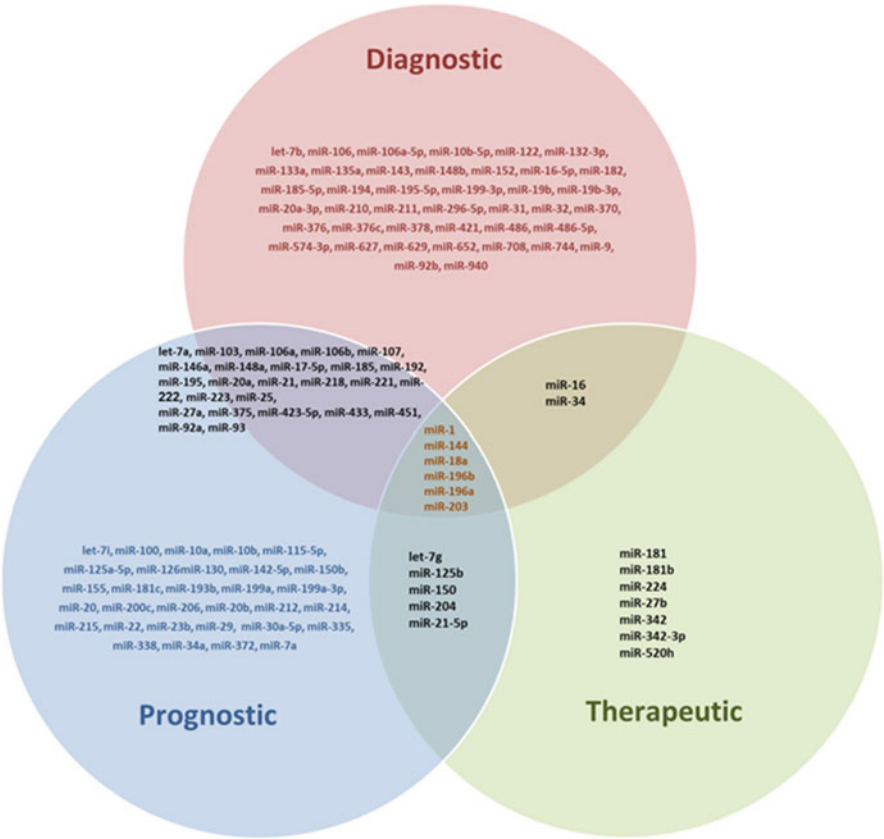

Fig. 6.3 Multifunctional role of miRNA biomarkers in gastric cancer

6.7 Conclusions

We have presented the role of miRNA in GC and their potential use as future diagnostic, prognostic, and therapeutic biomarkers. Apart from current conventional tumor antigens such as CEA, CA19.9, and CA72.4, there is an urgent and strong need for the development of novel biomarkers, single or in combination, with high sensitivity and specificity for the screening of GC. These miRNA-based biomarkers should further be explored exhaustively for clinical testing to facilitate the diagnosis, prognosis, and personalized treatment of the disease.

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